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# ANNALS OF INTERNAL MEDICINE

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## PARENTERAL SULFAPYRIDINE; THE INTRAVE- NOUS USE OF SODIUM SULFAPYRIDINE AND A REPORT OF CLINICAL AND LABORATORY OBSERVATIONS ON THE USE OF A GLU- COSE-SULFAPYRIDINE SOLUTION \*

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MARSHALL and Long<sup>1</sup> have recently reported observations on the intra-venous use of the sodium salt of sulfapyridine<sup>2</sup> in patients in whom it is desirable to attain high concentrations of sulfapyridine in the blood rapidly and in patients in whom oral therapy results in inadequate concentrations or entails undue discomfort. Since occasions similar to the ones they outlined frequently arise, and since under such conditions the procedure may be of life-saving value, further reports of the use of this compound seem justified. While the clinical findings reported in this paper with respect to sodium sulfapyridine are largely confirmatory, additional data are added concerning both the efficacy of this compound and its toxicity. The main subject of this paper, however, concerns clinical and laboratory investigations of a glucose-sulfapyridine solution which was prepared in an effort to obtain effective materials suitable for both intravenous and subcutaneous injection. The findings are reported in order to emphasize the importance of clinical and laboratory assay rather than to offer a new effective remedy.

### THE USE OF SODIUM SULFAPYRIDINE INTRAVENOUSLY

A summary of the more relevant data in each of 21 patients who received one or more intravenous injections of this compound is shown in table 1. For the most part these patients were suffering from severe acute infections, and the injections were given as a preliminary to oral sulfa-

\* Received for publication October 12, 1939.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

TABLE I  
Summary of Cases Treated with Sodium Sulfapyridine Intravenously

Sodium Sulfapyridine Intravenously													
Num- ber	Sex and Age	Diagnosis	Day of Disease	Amount (gm.)	Saline Diluent (c.c.)	Time for Injection (min.)	Blood Concentration			Reactions	Other Specific Treatment	Outcome	Remarks
							Time After End of Injection	Total					
								Free	Milligrams per 100 c.c.				
1	M 55	Meningitis (?)	?	3.2	600	60	2 minutes 3 hours	2.3 1.3	2.6 1.6	Restlessness increased during injection	S.P. 68 g. p.o. in 5 days	Recovered	Smear of spinal fluid: Gram + cocci. Cultures all yielded no growth. S.P. detected in urine 15 minutes after injection begun. Innumerable colonies in blood cul- ture before treatment; none after treatment.
2	F 74	Meningitis, Pn. XIX	7?	5.0	1500	150	2 minutes	10.5	10.5	None	S.P. 26 g. + P.A.B.S. 12 g. p.o. in 3½ days	Died	Blood culture positive before in- jection; was negative before oral drug was resumed.
3	M 14	L. Pneum., Pn. I	4	5.0	500	25	2 minutes	9.5	10.6	Diarrhea, vomiting; irritational	S.P. 20 g. p.o. (3 g. be- fore) in 3½ days	Crisis	Blood culture positive before treat- ment. Meningitis developed after 2½ days of oral therapy.
4	M 74	L. Pneum., Pn. XIV	28	5.0	500	60	15 minutes	9.1	9.8	None	S.P. 53 g. p.o. in 6 days	Died	Blood culture: <i>Staph. aureus</i> (twice). * 14 hours later, after 3 g. p.o.
5	M 49	B. Pneum., laryngi- tis, tracheotomy	9	5.0	1000	45	*	10.6	11.2	None	S.P. 10 g. p.o. in 3 days	Died	Pneumonia complicated nephritis with anasarca. Blood cultures positive. * 21 hours later, after 1.5 g. p.o.
6	F 18	B. Pneum., Pn. VIII Glomerular nephri- tis	4	5.0	500	60	—	—	—	None	Serum, 300,000 units; transfusions, 800 c.c.	Died in 16 hours	Pneumonia complicated nephritis with anasarca. Blood cultures negative * 21 hours later, after 1.5 g. p.o.
7	M 63	B. Pneum., Pn. V	7	5.0	300	30	*	5.0	8.1	Chill 1 hour after in- jection; auricular fibrillation	S.P. 36 g. p.o. in 5½ days	Crisis	* 20 hours later, after 4 g. p.o.; vomiting at this time. Injection interrupted because of reaction. Some extravasation with marked local reaction. Blood culture negative. Severe delirium tremens on second day of treatment. Negative blood cultures.
8	M 41	L. Pneum., <i>Str. hem.</i>	6	4.0	2000	120	—	—	—	Thrombosis both veins	S.P. 32 g. p.o. in 6 days	Lysis	
9	M 57	L. Pneum., Pn. III Delirium tremens	5	4.0 ±2.5	2000 250	120 25	—	10.6	11.0	Chill (?), convulsion, "collapse," fluttering respiration	None	Died in 2 hours	
10	M 42	L. Pneum., Pn. III Alcoholism, Jaun- dice	5	4.0	80	15	*	6.2	8.3	None	S.P. 6 g. in 30 hours	Lysis	

Abbreviations: M = male; F = female; L. = lobar pneumonia; B. Pneum. = bronchopneumonia; Pn. = pneumococcus (type is indicated by Roman numeral); S.P. = sulfapyridine; P.A.B.S. = sulfanilamide; p.o. = by mouth.

Cases 19, 20, and 21 were subjects of a more detailed study to be reported elsewhere.

TABLE I—Continued

Sodium Sulfapyridine Intravenously													
Num-ber	Sex and Age	Diagnosis	Day of Disease	Amount (gm.)	Saline Diluent (c.c.)	Time for Injection (min.)	Blood Concentration			Reactions	Other Specific Treatment	Outcome	Remarks
							Time After End of Injection	Free	Total				
11	M 70	L. Pneum., Pn. III Meningitis	? 4h*	4.0 4.0	100 100	15 10	2 hours Before 10 minutes 1 hour†	10.0 7.7 8.7 19.8 20.5 17.3 18.0	10.4 8.7 8.7 20.5 20.5 18.0 17.8	Vomiting, hiccup Pulmonary edema 3 hours after this in- jection	None	Died 12 hours after first injection	* 4 hours after the first injection. † Spinal fluid concentration at this time 5.7 and 6.7 mg. per 100 c.c. free and total, respectively.
12	F 76	L. Pneum., Pn. IV	?	4.0	1000	150	2 minutes	11.7 12.4	12.4	Restlessness increased, "collapse," Dizziness	None	Died in 6 hours	Blood cultures positive before and after treatment. Blood cultures positive for 10 days. Rb resaction.
13	F 52	L. Pneum., Pn. III Empyema	15	2.0	200	30	—	—	—	S.P. 114 g. p.o. 12 days before and 7 days after S.P. 4 g. p.o.	S.P. 114 g. p.o. 12 days before and 7 days after S.P. 4 g. p.o.	Recovered	
14	F 35	L. Pneum., Pn. I	8	4.0	80	20	*	5.0	8.7	None	S.P. 36 g. p.o. in 6 days begun 7 hours late S.P. 3 g. p.o. begun 2 hours later	Died in 18 hours	* Level 16 hours later, after S.P. 3 g. p.o. Blood culture positive on admission; negative before sulfapyridine injection. * Level at time nausea began.
15	M 22	Pulm. Tuberculosis B. Pneum. (?)	?	5.0	500	60	2 minutes 7 hours 5 minutes	3.7 8.3 3.7 9.7	3.8 8.6 5.6 10.4	Nausea after first 250 c.c. given in 10 min- utes None	S.P. 36 g. p.o. in 6 days begun 7 hours late S.P. 3 g. p.o. begun 2 hours later	Unim- proved Died in 10 hours	Concentration in spinal fluid 2 hours later = 3.7 free and 4.0 total; in stomach contents at this time = 33.2/33.2 mg. per 100 c.c. (before oral dose).
16	M 54	Meningitis, Pn. VII Alcoholism	?	5.0	500	90	30 minutes Before 2 minutes	9.9 7.4 8.9	11.8 8.9	None	P.A.B.S. 13 g. p.o. for first 3 days S.P. 40 g. p.o. in 5½ days, begun 24 hours after last injection	Recovered	* Hours after first injection. Pelvic abscess drained, multiple incisions with drainage of ab- dominal wall. Blood culture re- peatedly positive for <i>S. au.</i> after P.A.B.S. and before intravenous therapy, sterile after S.P. treat- ment.
17	M 27	Peritonitis and post- operative wound sepsis, <i>Staph. au- reus</i>	7 5h*	5.0 5.0	500 500	26 45	30 minutes Before 2 minutes 2 hours	11.8 7.4 8.9 18.2 18.9 14.6 16.3	11.8 8.9 8.9 18.2 18.9 14.6 16.3	None			
			11h*	2.5	250	45	Before 2 minutes	12.8 15.5 19.0	17.4 13.3 13.3				
			24h*	5.0	500	30	Before 2 minutes	11.7 18.4	13.3 20.8				
			31h*	2.5	250	30	Before 2 minutes	13.2 15.1	15.1 20.0				
			36h*	2.5	250	20	Before 20 hours	18.3 16.0	20.0 17.8				
			55h*	2.5	250	30		6.4	8.3				

TABLE I—Continued

Sodium Sulfapyridine Intravenously										Reactions	Other Specific Treatment	Outcome	Remarks
Num- ber	Sex and Age	Diagnosis	Day of Disease	Amount (gm.)	Saline Diluent (c.c.)	Time for Injection (min.)	Blood Concentration						
							Time After End of Injection	T Total					
								Free	Milligrams per 100 c.c.				
18	M 42	L. Pneum., Pn. I	2	5.0	500	50	10 minutes† 2 minutes 2 hours Before	7.7 7.9 7.9 7.5	7.7 9.9 9.9 7.5	Vomited after 10 min-utes (150 c.c. in-jected)—continued for several hours	Serum 100,000 units given 29 hours after first dose because of failure to show any response	Crisis 5 hours after serum	* Hours after first injection. † Af-ter beginning of injection when patient vomited—vomitus at end of injection had 8.9 mg. per 100 c.c. free and total sulfapyridine. Vomitus before second injection had 16.3 and 17.4 mg. per 100 c.c. free and total, respectively. Total of 2.67 g. recovered from urine in 30 hours. All blood cultures negative. * After beginning of injection (af-ter 250 c.c.). 30 minutes after be- ginning of injection had 33.4 and 36.4 mg. per 100 c.c. of free and total S.P., respectively. * After beginning of injection (af-ter 250 c.c.). Urine voided at this time had 4.7 and 6.3 mg. per 100 c.c. of free and total S.P., respectively. * After beginning of injection (af-ter 250 c.c.). Urine voided at this time had 9.0 and 10.0 mg. per 100 c.c. free and total S.P., respectively.
19	M 26	Gonococcal Arthri- tis	?	4.75	500	60	30 minutes* 2 minutes 5 hours 24 hours	7.7 9.9 7.7 8.0 3.5 3.7	7.7 9.9 7.7 8.0 3.5 3.7	Nausea at end of in-jection, lasted 6 hours	Misc. None for 3 days before or after this injection	Partly improved	
20	M 43	Arthritis, ? Gono- coccal	?	4.75	500	60	30 minutes* 2 minutes 5 hours 11 hours 24 hours	4.4 9.5 5.0 7.4 2.9 5.4 trace 3.2	5.3 10.3 7.4 5.4 3.2 5.4 trace 3.2	Anorexia, nausea and malaise for 4 hours	Misc. None for 3 days before or after this injection	Improved	
21	M 62	Parotid abscess, after erysipelas	?	4.75	500	60	30 minutes* 2 minutes 5 hours 11 hours 24 hours	5.1 9.8 5.7 7.6 3.2 5.3 trace 2.0	5.9 11.1 7.6 5.3 2.0 2.0	Dizziness for 1 hour after injection	Misc. None for 3 days before or after injection	Improved	

pyridine therapy. In two patients the injections were followed by specific serum therapy. The last three patients listed were not severely ill. They were the subjects of comparative studies on sulfapyridine and related compounds given by various routes.<sup>3</sup>

Sterile physiological salt solution was used as the diluent in every instance. The amounts of the drug in each injection varied from 2.5 to 5.0 grams. This was given in from 80 to 2000 c.c. of saline, or in concentrations ranging from 0.2 to 5 per cent. For the most part a 1 per cent solution was used, the larger volumes being reserved for dehydrated patients. When the drug was given in a volume of 100 c.c. or less, it was injected from a syringe in 10 to 20 minutes. Larger volumes were given by a slow drip, taking from one-half to two and one-half hours for the injection. One of the patients received seven injections, three were given two, and the others a single injection.

The maximum concentrations, attained a few minutes after the end of the initial intravenous injections of 4 or 5 grams of sodium sulfapyridine, ranged from 8.6 to 12.4 mg. per 100 c.c., of which from 0 to 17 per cent was determined as "combined" (acetylated) and the rest as free sulfapyridine.<sup>4</sup> In most of the subjects the concentration was about 10 mg. per 100 c.c. with about 7 per cent acetylated. The percentage of drug circulating as acetylated sulfapyridine after a single injection gradually increased as the total concentration dropped, but levels as high as 5 mg. per cent were usually still present 12 hours after the injection, and 50 per cent or more of this was "free" sulfapyridine. A more detailed account of the fate of the injected material in the last three subjects is given elsewhere.<sup>3</sup>

The drug was detected in the urine within 15 minutes after the beginning of an injection, and concentrations as high as 36 mg. per 100 c.c. were found in the urine after 30 minutes when only 2.5 grams had been injected with 250 c.c. of saline. The concentrations of the drug in the spinal fluid one hour after an injection in Case 11 and two hours after the injection in Case 16 were one-third and one-half of the corresponding blood concentrations, suggesting that the equilibrium between blood and spinal fluid is not reached very rapidly.

The stomach contents were studied in two patients during and after injection. In Case 16, a stomach tube was introduced for the purpose of further drug administration two hours after the intravenous injection, just after the lumbar puncture was completed. A small amount of the stomach content, withdrawn for analysis before any further drug was given, contained free sulfapyridine in a concentration of 33.2 mg. per 100 c.c. One patient (Number 18) began to vomit 10 minutes after the beginning of an injection. The concentration of drug in blood taken at this time from the opposite antecubital vein was 7.7 mg. per cent. At the end of the injection, the concentration of the drug in the blood was 9.9 mg. per cent and in the vomitus it was 8.9 mg. per cent. Five hours later the patient was still vomiting and the material brought up contained 17.4 mg. of sulfapyridine per 100 c.c., of

which 16.3 mg. were in the free form. At this time the level in the blood was 7.5 mg. These findings suggest that when sodium sulfapyridine is injected intravenously it is excreted rapidly into the stomach and may be concentrated there. Coupled with the fact that many patients receiving sulfapyridine orally began to vomit within a few minutes after the first dose, these observations would indicate that local gastric irritation may be an important contributing factor in the nausea and vomiting irrespective of any possible central effect of the drug.

As in Marshall and Long's cases, nausea with or without vomiting was the most frequent toxic effect observed. In our cases, this usually began during the course of the injection and lasted for several hours. In one patient the vomiting was associated with diarrhea and the patient became irrational and excited for a few hours. The vomiting, but not the mental symptoms, reappeared late when oral therapy was started. A second patient began to hiccup at the same time and this symptom continued until three hours after a second injection when he developed increasing pulmonary edema. At this time the blood level was 17.8 mg. per cent of which 14.8 mg. were "free" sulfapyridine.

One patient (Number 7) had a moderately severe chill which began an hour after the injection and lasted 15 minutes, during which time his pulse rate rose from 100 to 160 per minute and he developed auricular fibrillation. His rhythm reverted rapidly to normal after digitalization. Two patients complained of dizziness which began toward the end of the injection and lasted for about an hour. In another patient restlessness, which was present before the injection, increased during and after the administration of the drug, and this was soon followed by "circulatory collapse." Thrombosis of the veins into which the drug was injected occurred in two instances: In one (Case 8) both antecubital veins were involved and no other intravenous injections had been given; in the other (Case 17) a number of veins became thrombosed, but these had been used for various forms of intravenous medication, including the sodium sulfapyridine.

In Case 9, a reaction to the drug may have been the immediate cause of death. This was a patient with incipient delirium tremens who was apparently quiet when the injection was begun. After about 25 minutes, when approximately one-half of the material had been injected, he exhibited some generalized muscular activity and appeared to be having a chill. Before the needle was withdrawn a small amount of the solution had extravasated into the subcutaneous tissues. The patient soon had definite tonic and clonic convulsions, after which his skin became cold, ashen gray in color and moist. His respiration became irregular and fluttering in character, he became comatose and died within two hours after the beginning of the injection. In the interim, the tissues around the extravasated material became red, then markedly edematous and almost fluctuant.

In nine of the patients, including the one who received seven injections, there were no untoward reactions of any sort.

The therapeutic effect of the drug is difficult to assess in a group of such severe cases, particularly since other therapy was used in most of the patients. The four patients with pneumococcic meningitis all died. None of them received serum. Two died within 12 hours and the others after three or more days of oral sulfapyridine therapy. One of the latter (Case 4) was being treated for pneumonia and had clear spinal fluid two and one-half days after sulfapyridine therapy was begun. His blood culture showed 300 pneumococcus colonies per c.c. before the intravenous injection, and he had received 30 grams of sulfapyridine at the time when the diagnosis of meningitis was established. One patient, who may have had meningitis, recovered. His spinal fluid on admission to the hospital was turbid and showed numerous polymorphonuclear leukocytes; rare gram-positive cocci were seen in a smear of the sediment. However, cultures of this fresh fluid and of those obtained subsequently all yielded no growth.

Nine of the patients, excluding one with meningitis, had pneumococcic pneumonia. The blood culture was positive in five, of whom three died within 18 hours of the injection. One of the latter had severe glomerular nephritis and was also given specific serum. The only death among the four patients with sterile blood cultures was in the alcoholic Type III patient who had the convulsion during the injection.

Three cases are of special interest:

*Case 18.* A 42 year old man had Type I pneumococcus pneumonia and negative blood cultures. He received 10 grams of sodium sulfapyridine in two doses five hours apart. High concentrations were maintained for 29 hours without any appreciable effect on the course of the pulmonary infection. Crisis occurred five hours after the administration of 100,000 units of Type I antipneumococcic serum.

*Case 8.* A 41 year old man with lobar pneumonia had negative blood cultures, and hemolytic streptococci were obtained in almost pure culture from all the sputum specimens examined. He received two doses of four grams of sodium sulfapyridine intravenously 18 hours apart. Oral sulfapyridine therapy was begun eight hours after the second injection. He made an uneventful recovery except for thrombosis of his antecubital veins.

*Case 17.* A 27 year old man developed wound sepsis and peritonitis following an elective cholecystectomy. Blood cultures on two occasions during sulfanilamide therapy were positive for *Staphylococcus aureus*, prior to the first intravenous injection of sodium sulfapyridine. He was given seven injections of the latter drug over a period of two and one-half days, and then was given sulfapyridine by mouth. He was on Wangenstein drainage before and during the intravenous therapy because of persistent vomiting. Several abscesses of the abdominal wall and a large pelvic abscess were drained after several days, and the patient then made a slow but steady and uneventful recovery. It was felt that the institution of intravenous sodium sulfapyridine definitely marked the turning point in this patient who was failing rapidly and in whom, because of severe vomiting, effective oral therapy was impossible.

In another patient (Number 5) with *Staphylococcus aureus* bacteremia, associated with laryngo-tracheobronchitis and pneumonia, there was no effect from the drug. Tracheotomy had been done, and later additional oral therapy was given, but the patient died.

The observations on the clinical use of sodium sulfapyridine intraven-

ously may be summarized briefly. The drug was usually given slowly in four or five gram doses diluted to 1 per cent with physiological salt solution. High concentrations, usually 10 mg. per 100 c.c., were obtained rapidly in the blood, and these dropped rather slowly so that effective levels were still present six and sometimes 12 hours after a single injection. Acetylation began early and increased steadily. The drug appeared rapidly in the urine. In the spinal fluids, the concentration of the drug up to four hours after an injection was only one-half or less of the simultaneous blood level. The drug appeared rapidly in the stomach contents (withdrawn or vomited) and was found there in higher concentrations than in the blood. Reactions from the injections were usually of minor importance considering the severity of the cases treated. However, in one patient convulsions occurred during the injection and were rapidly followed by collapse, irregular respirations and death, and in a second the injections may have contributed to the early onset of pulmonary edema. The therapeutic value of the drug is difficult to assay because the number of cases is small and because additional therapy was given in most of the patients who were severely ill. In one patient with severe *Staphylococcus aureus* sepsis, the repeated intravenous injections of sodium sulfapyridine were probably life-saving.

#### GLUCOSE-SULFAPYRIDINE SOLUTION

Although it was found possible to maintain effective levels in some cases with two intravenous injections daily of sodium sulfapyridine, this material presented numerous undesirable features. The alkalinity of the solution offered the possibility of a sclerosing effect upon veins and of severe local necrosis resulting from accidental extravasation into the subcutaneous tissues. There was also the possibility of more than usual renal irritation<sup>5, 6, 7</sup> and of cerebral stimulation when large amounts of this material are rapidly introduced into the circulation. These considerations suggested the desirability of having the drug in a soluble non-irritative form that could be given subcutaneously in the necessary amounts with a convenient quantity of fluid. This would offer somewhat slower absorption, but, with adequate fluids, the drug could, if necessary, be mobilized more rapidly, thus overcoming Long's<sup>8</sup> objection to the oily suspensions suggested by Whitby.<sup>9</sup> The intramuscular injections of the sodium salt, especially where repeated large doses are necessary, did not seem desirable, although Gaisford<sup>10</sup> has used it by this route in 33 $\frac{1}{3}$  per cent solution, apparently without severe side effects.

The low solubility of sulfapyridine, which occasioned the introduction of the sodium salt, also led others to seek various methods of obtaining a stable solution of the drug in concentrations and in forms which are convenient for therapeutic purposes. Blake<sup>11</sup> succeeded in getting two grams of sulfapyridine into solution in a liter of fluid consisting of equal parts of 5 per cent glucose (in distilled water) and physiological saline which had been brought to a boil. This mixture then contained 0.2 per cent sulfapyridine which re-

mained in solution at room temperature for four days. He gave this solution intravenously, subcutaneously, and intrathecally, and was able to maintain high concentrations of sulfapyridine in the blood over considerable periods by such parenteral administration. We wished to obtain more concentrated solutions so that smaller volumes of fluid would suffice for parenteral use. It was found possible, by using more concentrated solutions of dextrose, to dissolve considerably larger amounts of sulfapyridine, but boiling became necessary to bring this about. The preparation of such solutions was then undertaken in the Research Division of the Lederle Laboratories, where it was found possible to dissolve upwards of 25 per cent sulfapyridine in 50 per cent dextrose. Solutions containing about 10 per cent sulfapyridine and 50 per cent dextrose in sterile ampoules were chosen, and these were supplied to us for clinical and laboratory studies. In the course of preparation and sterilization, these solutions assumed a slight golden brown color. These preparations were also supplied to Dr. Norman Plummer at Bellevue Hospital for independent studies.

*Clinical Observations.* The relevant data in 17 patients who received this solution by various routes are given in table 2. For the most part the solution was diluted 10 fold in physiological saline, so that the final concentration was 2 per cent sulfapyridine and 5 per cent glucose. The intravenous doses were usually injected in from 30 to 60 minutes, and the subcutaneous doses in one to three hours. One patient was given the original solution undiluted intravenously, and two others took it in this form by mouth. Each parenteral injection contained 50 c.c. of the original solution (equivalent to about five grams of sulfapyridine), except in some instances where the second or later doses contained only 25 c.c., or the equivalent of 2.5 grams of sulfapyridine.

The concentrations were determined by Marshall and Litchfield's method for sulfapyridine<sup>4</sup> just as in the previous cases. The significance of "free" (unconjugated) and "total" sulfapyridine as determined by this method in the present cases will be referred to below. After the intravenous injections of comparable amounts of glucose-sulfapyridine solution, the concentrations attained in the blood were appreciably higher than after comparable injections of sodium sulfapyridine. Within a few minutes after the injection of glucose solution containing five grams of sulfapyridine, the concentration in the blood determined as "total" sulfapyridine varied from 10.8 to 20.0 mg. per 100 c.c., of which from 6.6 to 100 per cent was determined as "unconjugated" sulfapyridine by the method used. These levels declined rapidly to one-half or less of the maximum concentration in two hours and to less than one-third in six hours. Only traces of drug were found in the blood after 12 hours. The maximum concentrations after single subcutaneous doses were attained from one to six hours after the injections and ranged from 3.6 to 6.6 mg. per 100 c.c., of which from 71 to 94 per cent was determined as free unconjugated sulfapyridine. The maximum concentrations from oral administration were attained 12 to 24 or more hours after ingestion and

TABLE II  
Summary of Relevant Data Concerning Patients Who Received Sulfapyridine-Dextrose Solution

Sulfapyridine Dextrose Administration															
Num- ber	Sex and Age	Diagnosis	Day of Disease	S.P.—50% Glucose Solution (c.c.)	S.P. Content (gm.)	Total Volume (with Saline Diluent) (c.c.)	Route	Time for Adminis- tration (minutes)	Sulfapyridine Concen- tration in Blood			Reactions	Other Specific Treatment	Outcome	Remarks
									Time After Administra- tion Ended	Free	Total				
1	M 17	L. Pneum., Pn. XXIII Sterile pleural effusion	3	20 20 10	2.0 2.0 1.0	0 0 0	p.o. p.o. p.o.	— — —	2 hours 2 hours 12 hours	— — —	Vomited before and after	None	Crisis same day	3 doses given 2 hours apart.	
2	M 26	Upper respiratory infection	1	20 20 10	2.0 2.0 1.0	0 0 0	p.o. p.o. p.o.	— — —	2 hours 4 hours 14 hours	— — —	Nausea 6 hours after last dose	None	Afebrile 1 hour after second dose	Doses 2 and 4 hours apart, respectively.	
3	M 34	L. Pneum., Pn. VIII	2	50	5.0	400	i.v.	60	10 hours	—	None	None	Lysis after 10 hours	—	
4	M 21	L. Pneum., Pn. V	4	50	5.0	500	i.v.	30	Before* 5 minutes 2 hours 11 hours 24 hours	— — — — —	None	P.A.B.S., 4 g. p.o., 4 days previously S.P., 11 g. p.o., in 2 days begun after 36 hours	Crisis, 30 hours after oral S.P.	* Sulfanilamide levels.	
5	F 74	B. Pneum., Pn. IV	6	50	5.0	500	s.c.	120	5 minutes 1 hour 7 hours 14 hours 2 hours 8 hours	— — — — — —	None	None	Lysis in 10-18 hours	Improving before treat- ment.	
6	F 52	L. Pneum., Pn. III Empyema	17	50	5.0	0	i.v.	30	2 hours 8 hours	— —	"Chilly," 5 min- utes after injec- tion, begun, no rise in tempera- ture	S.P. 44 g. p.o. before, 70 g. after this in- jection	Convales- cing	No S.P. for 3 days before and 9 hours after this injec- tion. Blood culture posi- tive before and after this injection.	
7	M 24	L. Pneum., Pn. XIV	3	50	5.0	500	s.c.	60	5 minutes 1 hour 3 hours	— — —	Nausea 3 hours later	S.P. 13 g. p.o. in 2 days. Begun 24 hours after last s.c. dose	Crisis 2 hours after first oral dose	S.c. doses given 12 hours apart. Marked improve- ment after last injection.	
			3½	25	2.5	300	s.c.	45	Before	—	None	—	—	—	—
			4	25	2.5	300	s.c.	60	Before	—	None	—	—	—	—

Abbreviations: M = male; F = female; L. Pneum. = lobar pneumonia; B. Pneum. = bronchopneumonia; Pn. = pneumococcus (type is indicated by Roman numeral); S.P. = sulfapyri-  
dine; P.A.B.S. = sulfanilamide; p.o. = by mouth; i.v. = intravenous; s.c. = subcutaneous; concentration + = trace.

TABLE II—Continued

Sulfapyridine Dextrose Administration													Outcome	Remarks		
Num- ber	Sex and Age	Diagnosis	Day of Disease	S.P.—50% Glucose Solution (c.c.)	S.P. Content (gm.)	Total Volume (with Saline Diluent) (c.c.)	Route	Time for Adminis- tration (minutes)	Sulfapyridine Concen- tration in Blood			Reactions				
									Time After Administra- tion Ended	Free	Total					
															Mg. per 100 c.c.	
8	M 67	B. Pneum., Pn. VII	5	50	5.0	500	s.c.	100	5 minutes 2 hours 6 hours 10½ hours 5 minutes 3 hours* 8 hours	2.3 4.4 5.4 3.4 3.4 2.6 +	2.5 5.4 5.8 4.8 4.2 3.3 1.6	Fluid absorbed slowly. Tissues swollen for 4 hours None	S.P. 9 g. p.o. in 2 days began 12 hours after s.c. dose  S.P. 39 g. p.o. in 6½ days; begun next day	Lysis 3 days later	Chill 5 hours after s.c. dose. Process in lung extended.	
9	M 18	L. Pneum. Pn. III Empyema	6	50	5.0	500	s.c.	180					None	S.P. 16 g. p.o. in 2½ days; begun 9 hours later	Lysis 2 days later	* Level in pleural exudate at this time = 1.8 (free and total). Closed tho- racotomy.
10	M 18	B. Pneum., Pn. XIII, Pn. XXVIII and Strep. hem.	?	50	5.0	500*	p.o.	—	1 hour 2 hours 3 hours 8 hours	0 +	1.5 2.2 2.9		None	S.P. 15 g. p.o. in 2½ days; begun 8 hours after second i.v. dose	Lysis 2 days later	* Tap water instead of sa- line.
11	M 50	Bronchiectasis, ? B. Pneum., Pn. VI	?	50	5.0	500	i.v.	30	2 minutes 2 hours Before*	11.8 4.1 2.3	15.4 5.6 3.1	Chill for 15 min- utes None	S.P. 15 g. p.o. in 2½ days; begun 8 hours after second i.v. dose	Improved and relapsed		# 2 doses i.v. 5 hours apart, then repeated 2 days later.
			+12	50	5.0	500	i.v.	30	5½ hours 2 minutes 2 hours Before*	15.8 2.7 9.8 16.7	20.4 3.8 10.0 6.6	None None	Second course of S.P. begun p.o. 2 days after last i.v. dose			
				50	5.0	500	i.v.	30	2 hours 2 hours 5 minutes 6 hours	7.4 4.3 13.3 3.5	8.0 4.8 14.3 4.2	None				
12	M 44	L. Pneum., Strep. hem. (?)	5	50	4.75	500	i.v.	30					None	S.P. 27 g. p.o. in 5½ days; begun 8 hours later	Lysis 2 days later	Fever for 2 weeks.

TABLE II—Continued

Sulfapyridine Dextrose Administration													Outcome	Remarks		
Num-ber	Sex and Age	Diagnosis	Day of Disease	S.P.—50% Glucose Solution (c.c.)	S.P. Content (gm.)	Total Volume (with Saline Diluent) (c.c.)	Route	Time for Adminis-tration (minutes)	Sulfapyridine Concen-tration in Blood			Reactions				
									Time After Adminis-tration	Free	Total					
															Mg. per 100 c.c.	
13	M 44	B. Pneum., Pn. XIV Bronchial asthma	3 3*	50 50	4.75 4.75	500 500	s.c. s.c.	50 45	5 minutes 3 hours 5 minutes 14 hours 15 minutes	4.6 4.8 7.5 1.7 6.3	4.8 5.6 8.1 2.1 7.1	None    None	None	Lysis 2 days later	Second s.c. dose 4 hours after the first; third injection 14 hours after the second. Pneum. began during asthmatic attack. First s.c. dose at end of i.v. dose, second one 6 hours later. Fever unaffected. This case and the two that follow were chosen for absorption and excretion studies which are reported in detail elsewhere. <sup>3</sup> They are the same as Numbers 19, 20 and 21, respectively, in Table I.	
14	M 37	Encephalitis (?)	?	50	5.0	500	i.v.	60	60	—	—	—	None	None	Died 2 days later	
15	M 26	Gonococcal Arthri-tis	?	50	4.75	500	i.v.	60	60	12.9	15.5	None	Misc. None for 3 days before or after	Improved		
			+3	50	4.75	500	s.c.	60	6 hours	1.6	1.9	None				
			+6	50	4.75	500	p.o.	60	1 minute 6 hours 5 minutes 24 hours	3.0 6.2 1.5 5.0	3.3 6.6 1.8 5.6	Nausea, from 2 to 7 hours				
16	M 42	Arthritis, (?) Gonococcal	?	50	4.75	500	p.o.	60	5 minutes 24 hours	+	+	None	Misc.			
			+3	50	4.75	500	i.v.	60	1 minute	18.4	20.0	None				
			+6	50	4.75	500	s.c.	60	1 minute	2.2	2.3	None				
				50	4.75	500	s.c.	60	6 hours	2.9	4.1	None				
			?	50	4.75	500	s.c.	60	1 minute	2.4	3.0	None				
				50	4.75	500	i.v.	60	6 hours	3.0	3.5	None				
			+3	50	4.75	500	p.o.	60	1 minute	13.4	16.0	None				
			+6	50	4.75	500	p.o.	60	6 hours 5 minutes 24 hours	2.4 2.4 2.5	2.6 2.4 3.9	None				
17	M 62	Parotid Abscess		50	4.75	500							Misc.			

varied from 2.9 to 5.6 mg. per 100 c.c., of which from 55 to 89 per cent was in the "free" form. In one patient with empyema the pleural fluid obtained three hours after a subcutaneous injection had a concentration of 1.8 mg. of drug (free and total) and the blood at this time had 3.3 mg., of which 2.6 mg. were determined as free sulfapyridine.

Untoward reactions from this solution were considerably less than after the sodium salt. There were no venous thromboses noted and there was no discomfort whatever from the subcutaneous injections. One patient vomited both before and after taking the solution by mouth. Three other patients had nausea, two after oral and one after subcutaneous doses, and in each instance this symptom began two hours or more after the drug was given.

The cases treated with the glucose sulfapyridine solution were considerably milder than those treated with the sodium salt. One patient (Number 2) had symptoms suggesting the onset of pneumonia and had a critical drop in temperature and subsidence of symptoms within a few hours after taking the solution by mouth, but neither physical findings nor roentgen-ray examinations showed any pulmonary involvement. In three patients with pneumonia (Numbers 1, 3, and 5) the drug appeared to be efficacious, since there was rapid recovery within a few hours after its administration and no other specific therapy was used. Each of these patients had received the drug by a different route. In most of the other patients with pneumonia, the subsequent administration of sulfapyridine orally made a proper estimation of the value of the glucose solution difficult. However, none of the cases with typical pneumonia showed definite improvement before the oral sulfapyridine therapy was begun, although the equivalent of from 5 to 15 grams had already been given parenterally in the form of the glucose solution, and all recovered rapidly after receiving tablets of sulfapyridine orally. These findings suggested that the effect of the material that we were giving in glucose solution was not very striking and was certainly not equivalent to the effect to be expected from corresponding amounts of sulfapyridine or of its sodium salt.

#### CHEMICAL AND BACTERIOLOGICAL INVESTIGATIONS

Detailed comparative studies were undertaken in each of three subjects to determine the blood concentrations and the urinary excretion of single comparable doses of the glucose-sulfapyridine solution and sulfanilamide given orally, subcutaneously and intravenously, of sodium sulfapyridine given intravenously, and of sulfapyridine given orally. Studies were also made to determine the bactericidal action of these substances when added *in vitro* to cultures or to human blood, and similar studies were carried out with the blood of patients after the administration of these substances by various routes. The results are reported in detail elsewhere.<sup>3,12</sup> Certain of the observations bearing on the clinical findings presented may be summarized briefly.

Following the intravenous injection of a single dose of glucose-sulfapyridine the concentration of sulfapyridine attained in the blood is considerably greater than after the intravenous injection of the same amount of sodium sulfapyridine. The blood concentrations fall much more rapidly after the glucose solution than after the sodium salt. The latter, in turn, behaves like sulfanilamide. The kidney clears the glucose sulfapyridine at a rate several times that of either sodium sulfapyridine or of sulfanilamide. Indeed, the clearance of the glucose sulfapyridine given intravenously is so high as to suggest that there is no reabsorption by the tubules. This is in sharp contrast to the low clearances found after the intravenous injection of sodium sulfapyridine or of sulfanilamide which indicate considerable reabsorption of the "free" and some reabsorption of the acetylated forms of the latter compounds. The difference between the clearances of glucose sulfapyridine and of sulfanilamide was in nowise altered when the subcutaneous route was used. The blood levels attained were lower after the subcutaneous injection but in each instance they were more sustained.

Following the oral administration of the glucose-sulfapyridine, absorption is considerably delayed so that the maximum levels in the blood are reached after 24 and sometimes even after 36 hours, in contrast to four or six hours after ingestion of sulfapyridine or sulfanilamide. The levels are somewhat lower than with the two latter compounds. The results obtained for clearances when the glucose sulfapyridine is taken by mouth are essentially the same as for sulfapyridine or sulfanilamide, and not like that of glucose-sulfapyridine given parenterally.

These findings are indirect evidence that at least most of the sulfapyridine found in the blood after intravenous or subcutaneous injection of the glucose sulfapyridine solution is circulating in a different form from that found after the oral ingestion of the same material. Presumably, in the former instances the sulfapyridine is chemically combined with glucose and when it is absorbed from the bowel the compound has been hydrolyzed, leaving sulfapyridine free to act as such. Unfortunately, if this is true the method used for determining free sulfapyridine would involve hydrolysis of the compound giving values for the determination of "free" sulfapyridine, which would include any of the drug that is in combination with glucose. Furthermore, acetylation of sulfapyridine proceeded in a different manner when glucose-sulfapyridine was given by the intravenous or subcutaneous routes than when it was given orally. In the latter instance it behaved like sulfapyridine or sulfanilamide. Additional evidence indicated that the glucose sulfapyridine, when given intravenously and subcutaneously, did not distribute itself in the body fluids to the same extent as sulfanilamide or as sodium sulfapyridine.

The urine collected after parenteral glucose-sulfapyridine administration contained both free and conjugated sulfapyridine by the method used. Although large concentrations of the conjugated form were found in the urine, this was probably not the glucose compound, since it is not hydrolyzed in the

course of determining the amounts of free sulfapyridine and is not accompanied by glycosuria.

The bacteriological tests indicated that when sodium sulfapyridine is added to human blood it exerts marked pneumococcal activity and behaves, in this respect, like equivalent amounts of sulfapyridine.<sup>12</sup> The glucose-sulfapyridine, on the other hand, showed no bactericidal or bacteriostatic activity even when high concentrations were used. When glucose sulfapyridine was added to blood and the mixture allowed to stand at room temperature, or better at 37° C., and then tested, it was found to exert bacteriostatic activity equivalent to that found with smaller concentrations of sulfapyridine. Blood withdrawn from patients after parenteral administration of the glucose-sulfapyridine solution showed no bactericidal or bacteriostatic action when tested, but, just as in the *in vitro* experiment, slight bacteriostatic action developed after standing. After the oral ingestion of this material, however, the bactericidal action of the blood was the same as that found with similar blood concentrations after the administration of sulfapyridine or its sodium salt, and corresponded to the level of free sulfapyridine in the blood.

These findings indicated that the sulfapyridine as it occurred in the glucose-sulfapyridine solution or in the blood after the parenteral injection of this solution was, for the most part, inert. The sulfapyridine found in the blood after oral ingestion was active and probably uncombined with glucose. Active material is also released when glucose-sulfapyridine is allowed to stand in freshly shed blood.

### CONCLUSIONS

Sodium sulfapyridine given intravenously is of therapeutic value and may be life-saving in selected cases. Its administration is frequently accompanied by toxic reactions, some of which may be serious.

A highly concentrated solution of sulfapyridine in 50 per cent glucose was found to be non-toxic when given parenterally. When thus given, however, it was mostly inert, whereas after oral administration it behaved like sulfapyridine, except that its absorption was delayed.

Careful clinical and biological control is just as important when new methods of administration are used for chemicals of known efficacy as when new chemicals are introduced.

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## THE TREATMENT OF LOBAR PNEUMONIA WITH SULFAPYRIDINE AND SODIUM SULFAPYRIDINE, WITH OBSERVATIONS UPON EFFECTIVE BLOOD LEVELS \*

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SINCE the demonstration by Whitby<sup>1</sup> of the specific action of sulfapyridine against the pneumococcus, the value of this new chemotherapeutic agent in the treatment of lobar pneumonia has been the subject of extensive clinical investigation. The report of Evans and Gaisford,<sup>2</sup> describing the results of treatment of 100 patients ill with lobar pneumonia, was so impressive that a stimulus was given for a wide-spread trial of the drug in this country. Subsequent publications,<sup>3-7</sup> already voluminous, not only have confirmed the observations of Evans and Gaisford, but have established a definite place for sulfapyridine in the treatment of pneumococcus lobar pneumonia. It has been shown that the drug is effective in all types of pneumococcus pneumonia, bringing about in most instances, a rapid decline in the patient's temperature and pulse rate, and that the case fatality rate is appreciably lowered in bacteremic as well as in non-bacteremic patients. Certain toxic reactions have been encountered, notably nausea and vomiting, toxic hepatitis, hematuria, kidney stones, nitrogen retention, anuria, drug rashes, as well as central nervous system disturbances. Although distressing and sometimes severe, they have not seriously interfered with the extensive clinical use of the drug.

A satisfactory system of dosage has been difficult to establish, owing to the irregularities of absorption of sulfapyridine. Long and Feinstone,<sup>8</sup> and Stokinger<sup>9</sup> have shown that absorption from the gastrointestinal tract is slow and varies markedly among different persons on the same dosage schedule. Because of this, Long<sup>10</sup> has stated that "it is best to discuss dosage in terms of concentration of the drug in the blood." In his experience, blood concentrations of 4 to 6 mg. per cent during the first three or four days of treatment are recommended for patients moderately ill with pneumococcus pneumonia. Blood levels of 7 to 10 mg. per cent are advised for severely ill patients.

In an effort to maintain satisfactory blood concentrations, various attempts have been made to introduce the drug parenterally. Whitby<sup>11</sup> has

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described the subcutaneous or intramuscular injection of sulfapyridine in oily suspension. Barnett and his co-workers<sup>12</sup> gave the sodium salt of sulfapyridine in a 2 per cent solution by rectum to patients with pneumonia, and were able to maintain "adequate blood concentrations." Marshall and Long<sup>13</sup> were the first to publish their results on the use of sodium sulfapyridine intravenously in human beings. They recommend the giving of this salt in a 5 per cent solution at five-hour intervals to severely ill patients.

The present report records observations made on 135 patients ill with pneumococcus pneumonia. There were 110 patients treated with sulfapyridine alone; and 25 patients given sodium sulfapyridine in combination with sulfapyridine orally. We have made an attempt to determine the optimum drug concentration by a study of the blood levels achieved in the course of routine administration of sulfapyridine. We will briefly record our experiences with these drugs.

#### MATERIALS AND METHODS

In November 1938, we began the treatment of patients with sulfapyridine under the Pneumonia Control Program sponsored by the District of Columbia Health Department. The cases included in this study were for the most part treated at the Gallinger Municipal Hospital. A large number received treatment at the Emergency Hospital, under the Parmelee Pneumonia Study. A smaller number of patients were treated in other hospitals of Washington or in homes. All of the patients, however, were observed by one of us at daily intervals. Each patient was studied according to the routine of the Program, which consisted of a complete history, physical examination, sputum typing and blood culture, hemogram, and urine analysis, as well as roentgen-rays whenever possible. Blood counts were taken at frequent intervals, and blood cultures repeated as indicated. Daily blood sulfapyridine determinations were made on many of the recent cases. Treatment was instituted only after a satisfactory sputum typing had been accomplished.

Owing to the limited supply of the drug on hand when this study was begun, a certain selection of cases was necessary. Accordingly, alternate patients with Type I pneumococcus pneumonia were given type-specific horse or rabbit serum. A few patients with pneumococcus pneumonia caused by the "higher types" were given rabbit serum sent to us for experimental trial. A total of six patients were given type-specific antiserum in addition to sulfapyridine and are the only serum-treated cases included in this study. All other patients, irrespective of type, received the drug.

When a supply of sodium sulfapyridine became available, this was given intravenously in conjunction with sulfapyridine orally. Twenty-five patients received the former drug according to the technic recommended by Marshall and Long.<sup>13</sup> In some instances sodium sulfapyridine was given prior to commencing oral therapy, in order to study the blood concentration. On other occasions it was given subsequent to oral therapy when the blood levels were found to be low.

At the beginning of this study, sulfapyridine was given in initial doses of 2 grams statim, followed by 1 gram at four-hour intervals, until the temperature had been normal for 48 to 72 hours. The initial dose was subsequently increased to 4 grams and the drug continued as before during the critical period. After 48 to 72 hours the drug was reduced to 1 gram every six hours, maintained at this for another 48 to 72 hours, then further reduced to 0.5 gram every four hours for a similar period.

Sodium sulfapyridine was given intravenously as a 5 per cent solution in distilled water or physiological saline. The usual dose administered to an adult of average size was 3.8 grams. For undersized individuals, 0.05 gram per kilogram of body weight was the dosage adopted. The solution was administered slowly over the course of 10 to 12 minutes, care being taken that none of the material escaped outside the vein.

Blood sulfapyridine determinations were made by Marshall's method, previously described for sulfanilamide.<sup>14, 15</sup>

There were 122 patients in whom a diagnosis of pneumococcus lobar pneumonia was made, and 13 patients in whom bronchopneumonia, or atypical pneumonia, was found. Atypical pneumonias of possible virus etiology have been excluded from this series.

### RESULTS

*Age Group, Sex, Race:* In table 1 are given the age, sex, and race distribution of the 135 cases studied. The frequency of pneumococcus pneumonia in the younger age groups, and in males, is demonstrated. The preponderance of colored over white patients must be qualified by annual census figures from Gallinger Municipal Hospital. These have shown a ratio of 60-40 in favor of colored patients.

TABLE I  
Distribution of 135 Cases According to Age, Sex, Race

Age	Sex and Race
10-19.....14 cases	Male white.....33 cases
20-29.....32 cases	Male colored.....53 cases
30-39.....35 cases	
40-49.....22 cases	Female white.....25 cases
50-59.....14 cases	Female colored.....24 cases
60-69.....10 cases	
70-79.....6 cases	
80-89.....2 cases	

*Incidence of Types, Bacteremia, Deaths:* There were 114 patients in whom a single pneumococcus type was isolated from the sputum. In 21 additional patients more than one type was obtained by the Neufeld reaction. Because of the difficulty of classification, these have been included in table 2 under a separate heading. The frequency of pneumococcus types found in this series correlates closely with previous findings of Dowling and Aber-

nethy.<sup>16</sup> Of interest is the fact that Type II is relatively infrequent as a cause of pneumococcus pneumonia in Washington. In the majority of instances, Types I to VIII pneumococcus were found, 58 per cent of the cases being caused by these types.

TABLE II  
Incidence of Types, Bacteremia, Deaths

Type	No. Cases	Bacteremia	Deaths
<i>Single Types</i>			
I.....	23	7	0
II.....	7	2	1
III.....	22	2	2
IV.....	8	2	1
V.....	1	0	0
VI.....	2	0	0
VII.....	8	2	0
VIII.....	8	2	2
IX.....	3	0	0
X.....	2	0	0
XI.....	1	0	0
XII.....	1	0	0
XIII.....	2	0	0
XIV.....	5	0	1
XV.....	1	0	0
XVI.....	2	0	1
XVII.....	1	1	0
XVIII.....	4	1	1
XIX.....	3	0	0
XX.....	1	0	0
XXI.....	3	0	1
XXII.....	3	1	3
XXIV.....	2	0	0
XXVII.....	1	0	0
<i>Multiple Types</i>			
IV, VI.....	1	0	0
XVI, XX, XXXI.....	1	0	0
III, VII, XXI.....	1	0	0
XVII, XXXII.....	1	0	0
XXIX, XIV.....	1	0	0
X, XIII, XXVIII.....	1	0	0
III, X, XI, XVI, XVII.....	1	0	0
III, VIII.....	1	0	0
XII, XVIII.....	1	0	0
XVIII, XIX, XXI, XXIII, XXV.....	1	0	0
VI, XVIII.....	1	0	0
III, XI, XVI.....	1	0	0
I, VII, XX.....	1	1(XX)	1
IX, XIII.....	1	0	0
XVIII, XI, XX.....	1	0	0
VII, XIII.....	1	1(XIII)	0
VII, VIII.....	1	1(VII)	0
XIV, XV.....	1	0(VIII)	0
III, XVII.....	1	0	0
III, XIX.....	1	0	1
III, IX.....	1	0	0
Total.....	135 Cases	23 Bacteremia	15 Deaths

% Bacteremia (among 122 cases).....18.8%  
% Died.....11.1%

Blood cultures were taken on 122 patients. In 23 of these, bacteremia was discovered (18.8 per cent). This low incidence may be explained in part by the fact that most of these cultures were transferred for study to the Health Department laboratory, which is located some distance from the Municipal Hospital. We do not believe that the cases seen in Washington during the past season were any less severe than in former years.

There were 15 deaths in this series, or a case fatality for the whole series of 11.1 per cent. No patients were excluded from the study because of insufficient treatment. The proportion of deaths among 99 non-bacteremic cases was 8 per cent; among 23 bacteremic cases, 21 per cent. An analysis of the deaths is given in table 3.

*Effects of Therapy on the Clinical Course:* As have others,<sup>3-7</sup> we found a rapid fall in the temperature and pulse rate with sulfapyridine. In 93 patients the temperature fell by crisis to 100 degrees in an average time of 16 hours from the beginning of therapy. This group includes cases treated early as well as late in the course of the disease. In 23 patients defervescence occurred by lysis over a period of 48 hours or longer. In 19 patients we were unable to observe that the drug exerted any beneficial effect upon the febrile course of the disease. Although, in most cases, with the decline in temperature there was a rapid amelioration of symptoms, these findings were not so constant as seen in patients treated with type-specific serum. We would agree with Finland<sup>7</sup> that patients treated with sulfapyridine alone manifest evidence of illness for a considerably longer period of time. It has not been unusual, in our experience, to observe symptoms of intoxication which persist for two to four days after the temperature has become permanently normal.

We have seen numerous instances of rapid resolution of the pneumonic consolidation. In other instances resolution has proceeded at an unusually slow rate. Similar to the findings of others, we have observed six cases of relapses or recurrence occurring when the dosage was reduced before resolution was well advanced. In addition, we have seen reinfection with a different type of pneumococcus in three patients, within four to six weeks after complete recovery from the original attack of pneumonia. Our data on the immune response of patients treated with sulfapyridine alone indicate that type-specific immunity for the infecting pneumococcus develops at or about the time of recovery.

*Dosage:* The amount of drug given each patient varied considerably, depending upon the presence or absence of toxic symptoms and the clinical response elicited. In the early part of this study a dosage of 2 grams was given initially. In the more recent cases, where particular attention has been paid to blood concentration, larger doses have been given initially (4 grams) and oral therapy has been supplemented with intravenous injections of sodium sulfapyridine. The average total dosage given to these 135 patients was 29.6 grams.

*Complications:* Six patients developed pleural effusion during or sub-

TABLE III  
Analysis of Deaths

No.	Age	Type	Bact.	No. Lobes Involved	Adm. W.B.C.	Day of Adm.	Day Rx Begun	Total Dosage Grams	Remarks
1	45	IV	0	1	12,000	1	4	21	Fractured skull. No response to Type IV rabbit serum.
2	61	XXI	0	2	6,400	1	4	4	Bronchopneumonia following operation for cancer stomach. Co-existing tbc.
3	45	XIV	N.D.*	1	28,000	6	6	5	Uremia.
4	15	XVI	0	2	18,000	1	4	8	Congenital heart disease with congestive failure.
5	23	XXII	0	1	7,000	3	4	25	Anemia before treatment, accentuated by sulapyridine.
6	53	VIII	0	2	30,000	7	8	30	Diabetes, hypertension. No response to 240,000 U. rabbit serum.
7	40	XXII	+	3	22,600	6	7	21	C-V renal disease. Uremia.
8	43	II	0	2	25,300	6	8	50	Rheumatic heart disease. Congestive failure.
9	66	I, VII, XX	+	3	15,000	6	10	63	No response to Type I or VII serum. Developed empyema.
10	75	III	+	2	6,600	2	2	12.2	C-V renal disease, circulatory failure during serum administration.
11	70	XVIII	N.D.*	2	13,000	5	5	4.8	Moribund on admission. Uremia.
12	52	III, XIX	0	1	22,000	?	?	7.6	Moribund on admission. Uremia.
13	32	VIII	+	3	9,350	1	10	33.6	Delirium tremens. No response to 900,000 U. rabbit and horse serum.
14	55	XXII	0	2	13,000	5	5	20.3	Congestive heart failure. ? Underlying tuberculosis.
15	39	II	+	1	?	2	3	6	Moribund on admission.

\* Blood culture not done.

sequent to their acute febrile period of illness (an incidence of 4 per cent). Diagnostic thoracentesis was performed in these patients as soon as the fluid was detected by physical examination or roentgen-ray. Subsequent removal of the fluid was performed as indicated by the clinical condition of the patient. If respiratory embarrassment was present, an attempt was made to remove all of the fluid. Empyema occurred in five patients (incidence of 3.7 per cent). The pneumococcus types isolated from these empyemata were: Types V, VII, IX, XVII and XX. It is interesting to note that in none of the 23 cases of Type I pneumonia did empyema develop. No other complications were present in this series.

#### OBSERVATIONS UPON BLOOD CONCENTRATION

In 65 of the 135 treated cases, observations have been made upon the blood levels. These were made in the majority of instances at daily intervals during the acute febrile period and up to the time convalescence was established. A total of 250 separate determinations of the "free" sulfapyridine concentration in the blood was made, or an average of almost four determinations per patient.

A correlation of the mean blood concentration with the clinical response obtained has been attempted. In table 4 are summarized the therapeutic effects according to certain groupings of the mean blood levels.

TABLE IV  
Relationship of Clinical Response to Mean Blood Concentration

Blood Concentration	Number of Patients	Recovered	Died	Clinical Response			
				Crisis	% Crisis	Lysis	No Effect
Group I—0-2.9 mg. %	18	17	1	13	66	3	2
Group II—3-5.9 mg. %	27	24	3	17		5	5
Group III—6-8.9 mg. %	13	12	0*	13*	90	0	0
Group IV—9-11.9 mg. %	7	6	1†	5		1	1†

\* Includes one patient who obtained excellent response to drug, but died later of cardiac failure.

† Denotes patient with diabetes and severe Type VIII infection. Obtained no response to serum or drug.

It will be seen that the largest number of patients are included in Groups I and II, those whose mean blood levels were 5.9 mg. per cent or below. A large number of recoveries took place in these two groups of patients, which corresponds to the findings of other investigators<sup>5-7</sup> who have reported excellent clinical improvement in patients whose blood levels were low. The number of recoveries was also large in Groups III and IV, where the mean blood level was 6 mg. per cent or above. There were fewer deaths in the latter two groups, only one of which could be attributed to failure of the drug.

The manner of clinical response demonstrated even more striking differences among the four groups. In Groups I and II there was the smallest percentage of patients exhibiting the phenomenon of crisis, and the largest number of those in whom the drug exerted little or no effect upon the temperature ("lysis" or "no effect"). By contrast, in those patients whose blood levels were 6 mg. per cent or above, there were only two whose response was not satisfactory. An explanation of the failure of patients to respond to sulfapyridine therapy was not clear in every case. In some patients nausea and vomiting interfered with absorption of the drug and, consequently, effective blood levels were not achieved. In others, complicating factors were present which might have interfered with the response. In some patients there was no obvious cause for the failure to achieve a satisfactory result. An analysis of these factors is given in table 5.

TABLE V  
Analysis of Cases Showing Poor Response to Therapy

Group	Case	Manner of Response	Remarks
I (0-2.9 mg. %)	1	Lysis	Nausea and vomiting.
	2	Lysis	Nausea and vomiting; leukopenia.
	3	Lysis	Pleural effusion.
	4	No effect	Diarrhea, anemia, pleural effusion.
	5	No effect	Moribund on admission.
II (3-5.9 mg. %)	6	Lysis	No obvious cause.
	7	Lysis	No obvious cause.
	8	Lysis	No obvious cause.
	9	Lysis	No obvious cause.
	10	Lysis	Pleural effusion.
	11	No effect	Nausea and vomiting; pleural effusion.
	12	No effect	Severe anemia; leukopenia.
	13	No effect	C-V-renal disease: uremia.
	14	No effect	Empyema.
IV (9-11.9 mg. %)	15	No effect	Empyema.
	16	Lysis	No obvious cause.
	17	No effect	Severe diabetes. No response to serum.

Although the number of cases in this series is small, the observations suggest that mean blood levels of 6 mg. per cent or above are desirable in patients being treated with sulfapyridine.

#### USE OF SODIUM SULFAPYRIDINE

While this work was in progress, Marshall and Long<sup>13</sup> reported upon the use of sodium sulfapyridine in 30 patients with pneumococcus pneumonia. Indications for giving this compound to patients were two-fold: first, the finding of low blood concentrations, usually the result of faulty absorption from nausea and vomiting, with poor clinical response; and second, unusual severity of the pneumococcus infection. They have shown that blood levels

of 5 to 8 mg. per cent can be attained with rapidity and maintained for at least four hours. In their experience, patients given sodium sulfapyridine intravenously, in combination with sulfapyridine orally, obtained excellent clinical responses.

A preliminary note of our use of this new compound in the treatment of 10 patients has been reported.<sup>17</sup> Up to the present time, we have given sodium sulfapyridine, in one or more intravenous injections, to 25 patients with pneumococcus pneumonia. These are included in the 135 cases reported above. This therapy has been supplemented with the oral administration of sulfapyridine.

A few of the early cases were given the sodium salt only after the previous administration of the oral preparation had resulted in low blood concentration or poor clinical response. The most recent cases have been given one injection of sodium sulfapyridine upon admission and sulfapyridine started by mouth simultaneously.

The type of response elicited in these two groups of patients is portrayed graphically in charts 1 and 2.

Chart 1 is the clinical record of a 29-year-old white male with Type I pneumococcus pneumonia of the right upper lobe. He was admitted to the hospital at the end of the first day of disease. Leukocytes were 29,700. The admission blood culture proved sterile. He was moderately ill. Oral sulfapyridine therapy was begun with 4.0 grams initially, followed by 1.0 gram at four-hour intervals. With administration of the third dose, he vomited a considerable portion of the previous medication and further oral therapy was temporarily stopped. Five hours after starting sulfapyridine therapy the blood concentration was only 1.1 mg. per cent, and by the following morning was 3.1 mg. per cent. There had been no appreciable effect upon his clinical course. He was then given 3.8 grams of sodium sulfapyridine intravenously. At the completion of injection the patient vomited. The blood level rose to 13.2 mg. per cent in five minutes, dropped progressively to 8.3 mg. per cent in one hour, 7.1 in three hours and 6.2 in seven hours. A second injection of sodium sulfapyridine was then given, with another prompt rise in the blood concentration to 13.3 mg. per cent and a gradual fall over a period of nine hours to 2.4 mg. per cent. After the first injection, there was a precipitous fall in temperature to 100.4° F. which was not sustained. After the second injection, the temperature fell to normal by crisis. Nausea and vomiting persisted for several hours. Convalescence was uneventful.

The patient represented in chart 2 was a 40-year-old colored female admitted to the hospital on the third day of disease. Consolidation of the lower left lobe was found. Pneumococcus Type II was obtained from the sputum by mouse inoculation. Blood culture proved sterile. The day after admission, the fourth day of disease, the patient was given 3.8 grams of sodium sulfapyridine intravenously. There was considerable nausea at completion of the injection, but no vomiting. The blood levels recorded were

9.4 mg. per cent in one hour, and 7.5 mg. per cent in four hours. Two grams of sulfapyridine were given orally at the beginning of this injection and continued in doses of 1.0 gram every four hours. During the course of this day the temperature fell by crisis to 100° F. in 12 hours. The following day the patient was given another injection of 3.8 grams intravenously be-

W. P. ♂. W. 29. Type I pneumococcus pneumonia

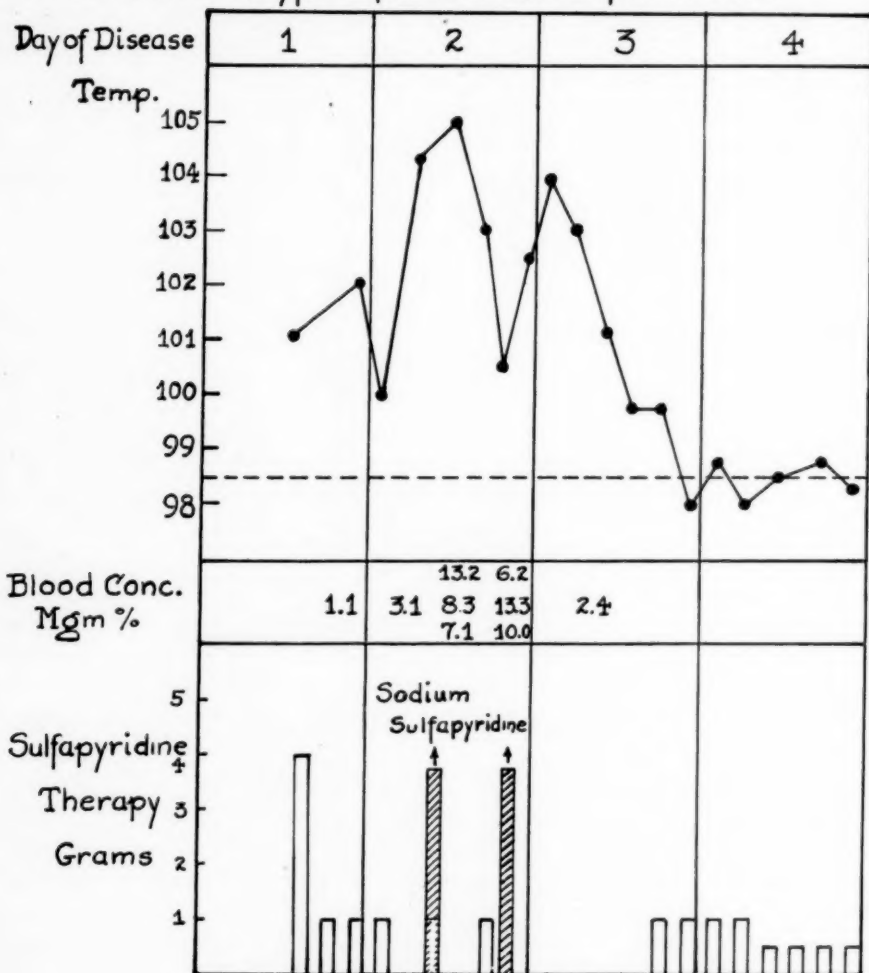
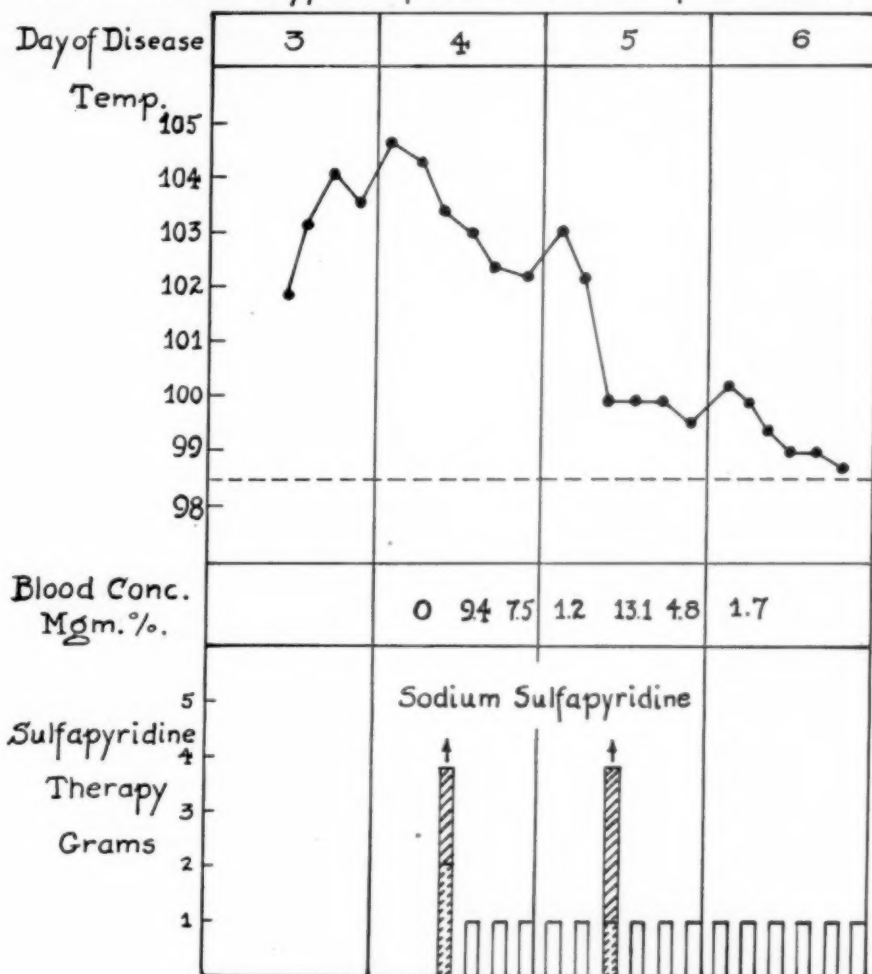


CHART I.

cause of the low blood level (1.2 mg. per cent), evidently the result of vomiting during the night. Following this second injection, there was again prompt rise in the blood level to 13.1 mg. per cent which fell to 4.8 in seven hours and was accompanied by marked clinical improvement. Sulfapyridine was continued during the next 48 hours, up to a total of 22 grams. The patient made an uneventful recovery.

A summary of our experiences with sodium sulfapyridine is given in table 6. A discussion of the toxic reactions to this salt will be given below. As yet, the number of cases so treated is too small to justify any statistical study of the case fatality rate. However, our observations have shown that

M.B. & C. 40. Type II pneumococcus pneumonia



## CHART II.

the intravenous administration of sodium sulfapyridine is an effective means of attaining high blood levels rapidly and that these can be maintained for several hours. The clinical response of patients who have received this drug is often dramatic.

TABLE VI  
Results of the Intravenous Injection of Sodium Sulfapyridine

Case No.	Color Sex Age	Type	Bact.	Dose	Blood Concentration—mg. per 100 cubic centimeters										Reactions	Remarks
					Be-fore	Time after end of injection							Later			
						5 min.	10 min.	20 min.	30 min.	1 hr.	2 hrs.	3 hrs.	4 hrs.			
1	W-M-36	V	0	3.8	4.0*		7.6	7.7	7.8						Nausea and vomiting Transient hematuria	Empyema—Recovery
2	W-F-14	I	0	3.0	6.4*		10.8							1.4, 1.0	Chill	Uneventful recovery
3	W-M-29	I	0	3.8 3.8	3.1* 6.2*	13.2 13.3				8.3	7.1 10.0			2.4	Nausea and vomiting None	Uneventful recovery
4	W-M-58	I	+	3.3	3.8*		16.7			11.0	9.6	8.8	12.4		None	Uneventful recovery
5	W-F-75	III	+	2.2	8.5*	*	21.4			14.1	14.0	13.8			None	Death during serum admin- istration
6	C-M-32	VIII	+	3.4	0†		6.8			6.0	5.7	5.5	5.9	5.6, 6.4 8.4, 6.0	None	Severe infection. Delirium tremens. 900,000 U. serum previously without effect. Death
7	C-M-29	I	0	3.9	0†		7.0			5.7	4.5	3.8	3.6	7.3, 3.2	None	Uneventful recovery
8	C-M-22	I	0	3.8	0†		7.8			17.18	7.4	3.6	3.8	3.6, 5.0, 2.4	Nausea and vomiting	Uneventful recovery
9	C-F-40	II	0	3.8 3.8	0† 1.2					9.4 13.1			7.5	4.8, 1.2, 3.6	Nausea and vomiting Nausea and vomiting	Uneventful recovery
10	C-M-44	III	0	3.8	0†					6.1			4.5	3.8, 3.9, 3.7 2.8	Nausea and vomiting	Uneventful recovery
11	C-M-45	I	0	3.8	0†					5.6			7.5	4.3, 3.6, 2.5	Slight nausea	Uneventful recovery
12	C-F-25	XIV	0	2.7	2.5*		6.5							2.2	None	Uneventful recovery

TABLE VI—Continued

Case No.	Color Sex Age	Type	Bact.	Dose	Before	Blood Concentration—mg. per 100 cubic centimeters										Reactions	Remarks
						Time after end of injection											
						5 min.	10 min.	20 min.	30 min.	1 hr.	2 hrs.	3 hrs.	4 hrs.	Later			
13	C-M-70	XVIII	0	3.8	0†		5.0			4.4					None	Moribund on admission	
14	C-F-30	IV	0	2.8	0†		8.0			6.0	6.0		5.1	1.8	None	Uneventful recovery	
15	C-M-35	IX	0	3.8	0†					3.5				2.3, 1.8 4.7, 4.0	None	Uneventful recovery	
16	C-M-33	XVI		3.5	0†		6.6			6.0			7.2	9.0, 9.0	None	Uneventful recovery	
17	W-M-34	XIX	0	3.8 3.8	0† 5.1		4.4			4.4				6.0	Slight nausea and vomiting	Uneventful recovery	
18	C-F-22	X	0	3.8 3.8	0†					8.0				8.9, 6.0	None	Uneventful recovery	
19	C-F-52	XIX	0	3.8 3.8	0		11.4			11.4	9.0 11.4		11.4		None	Moribund on admission	
20	C-M-58	VII	+	3.8	0*		4.8				4.2		4.0	5.1, 4.8, 3.8	None	Emyema, recurrence, recovery	
21	C-M-42	II	0	3.8 3.8	3.6* 8.9					8.9 8.9	10.0		6.1 5.7	5.7	Gross hematuria	Severe infection. No response 600,000 U. serum previous to drug therapy. Death.	
22	W-F-34	XIV, XV	0	2.6	0†		4.0			3.6			4.0	6.0, 7.2	Nausea and marked mental confusion	Uneventful recovery	
23	C-M-42	XIV	0	3.5 3.5	9.0									2.7, 10.0, 10.0	Nausea and vomiting	Uneventful recovery	
24	C-F-55	XXII	0	3.8	0					5.4			6.4	6.4, 9.0	None	Congestive heart failure on admission. Death	
25	C-M-35	II	0	3.0 3.0	0† 3.0		15.0			5.0 12.5	4.4	3.9	3.8 11.0	3.4 12, 10, 9.5	Slight nausea, vomiting None	Drop in PMN over course of 3 days from 87% to 29%	

\* Denotes sulfapyridine administered orally prior to injection of sodium salt.

† Denotes sulfapyridine administered orally simultaneously with injection.

## TOXIC REACTIONS

A summary of the toxic reactions noted in this series of 135 cases is given in table 7. The reactions encountered with the use of sodium sulfapyridine in 25 cases have been outlined above (table 6). Most of these findings have been previously described by others.<sup>5-7, 10, 13</sup> We have found gastrointestinal symptoms to be the most frequent reaction, occurring in 34.7 per cent of all cases. In those patients treated with the sodium salt, 10, or 40 per cent developed either nausea alone, or nausea with vomiting, following the injection of the drug. In our experience, sulfapyridine therapy has had to be stopped only rarely because of these gastrointestinal disturbances. Temporary discontinuance of the drug, administration of the crushed tablets in milk, the giving of aluminum hydroxide preparations after each dose, and the intravenous injection of 5 per cent or 10 per cent dextrose all have been of value in alleviating these unpleasant symptoms.

Mild reduction of the red blood cells and hemoglobin values were noted in four patients. These required no treatment. Severe hemolytic anemia developed in one patient with a preëxisting anemia, and was principally responsible for her death. Another patient developed an acute hemolytic anemia during therapy, which responded promptly to transfusion. Leukopenia and granulocytopenia were each observed in two patients. In none of these, however, did agranulocytosis occur.

TABLE VII  
Toxic Reactions in 135 Cases

Reaction	Number	Incidence—%
Nausea, alone . . . . .	15	11.1
Nausea and vomiting—mild . . . . .	17	12.5
—severe . . . . .	15	11.1
Diarrhea . . . . .	1	0.7
Hemolytic anemia—mild . . . . .	4	2.9
—severe . . . . .	2	1.4
Leukopenia . . . . .	2	1.4
Granulocytopenia . . . . .	2	1.4
Hematuria . . . . .	2	1.4
Toxic psychosis . . . . .	3	2.2
Dermatitis . . . . .	4	2.9
Drug fever . . . . .	3	2.2

In 14 of the most recent cases, determinations of the non-protein nitrogen were performed at daily intervals. An elevation of 10 mg. per cent above the normal (25–35 mg. per cent) was observed during the course of therapy in 11 of these patients, all of whom subsequently recovered. In one patient who was under observation for chronic glomerular nephritis and who developed a Type XVIII pneumococcus pneumonia, there was considerable nitrogen retention and exacerbation of nephritis when sulfapyridine therapy was instituted. The non-protein nitrogen rose from a level of 64 mg. per cent before therapy to 120 mg. per cent after nine grams of the drug had been given over a period of 48 hours.

Hematuria was noted in two patients, both of whom received sodium sulfapyridine intravenously. In one of these patients the hematuria was transient and did not interfere with subsequent recovery. The other patient developed hematuria seven hours before death, which may have contributed to his demise. No cases of kidney stones have been observed by us.

Cyanosis of an extreme degree was seen in eight patients (5.8 per cent), but because of the difficulty of evaluating this sign in the presence of pneumonia it has been omitted from the tabular summary. Toxic psychoses were observed in three patients and were thought to be due to the drug.

Dermatitis, characterized by a diffuse morbilliform eruption, was noted in four cases (2.9 per cent). This eruption, similar to that seen in cases treated with sulfanilamide, appeared 8, 11, 11 and 12 days, respectively, after the beginning of therapy, lasted 3 to 4 days, and in three instances was accompanied by an exacerbation of temperature.

#### COMMENT

The results of the above study, conducted over a period of eight months, demonstrate the value of sulfapyridine in the treatment of pneumococcus pneumonia. The mortality rate of 11.1 per cent for the entire series of 135 cases is at variance with other published reports. Pepper and colleagues<sup>6</sup> have shown a mortality of 7 per cent among 400 cases of typed pneumococcus pneumonia. Finland et al.<sup>7</sup> found a case fatality rate of 15 per cent in 95 patients of a comparable age group. Although these variations have been found, it should be noted that each of these studies represents less than one year's experience. Not until the drug has been given over several seasons to considerably more cases will a figure representing the true case fatality rate be obtained. We believe, however, that in the future, unless critical attention is paid to the diagnosis of pneumonia and to the proper selection of patients for treatment, a false and too optimistic view of the therapeutic effects may result.

A comparison of sulfapyridine treated cases with those receiving type-specific serum is outside the scope of this communication. Such an analysis will be the subject of a subsequent report. Suffice it to say that the results here obtained compare favorably with those found in our serum-treated cases. It is interesting to note that in the period covered by this study, there were no deaths in 23 Type I cases. In the period between January 1 and September 1, 1938, there were 32 Type I patients, studied under the District of Columbia Pneumonia Control Program, who received specific serum treatment.<sup>18</sup> Two of these patients died, giving a case fatality rate of 6.2 per cent. In 16 untreated patients observed simultaneously the mortality rate was 25 per cent.

Although there is a uniformity of opinion among various authors as to the method of administration of sulfapyridine, there is considerable variation in the views concerning what constitutes the optimum blood level of the drug.

Pepper et al.<sup>6</sup> have stated that simple blood level determinations have limited value because of the fact that they have observed clinical improvement in patients whose level did not exceed 2 mg. per cent. Long,<sup>10</sup> on the basis of equally wide experience, has advised keeping the blood concentration between 4 and 6 mg. per cent during the first three or four days of treatment in order to achieve the best results. On the basis of our observations we believe that frequent blood level determinations are of definite value in the treatment of these cases. Notwithstanding the fact that certain recoveries do take place in patients whose blood levels are low, we believe that results are more satisfactory if the mean blood concentration is 6 mg. per cent or above. A significant difference between the clinical response of patients having high and those with low blood levels has been shown. Whereas 90 per cent of patients with mean blood concentrations above 6 mg. per cent recovered by crisis, only 66 per cent of those with levels below 6 mg. per cent recovered in this manner. The importance of similar correlation studies between blood level and recovery is obvious.

Our studies on the soluble salt, sodium sulfapyridine, have shown that this drug is of value as a supplement to the oral administration of sulfapyridine. The rapidity with which high blood concentrations can be attained makes it particularly useful in severely ill patients in whom a speedy therapeutic effect is desired. In patients whose blood levels are low and who are not responding to the oral preparation, it is a valuable therapeutic addition. Although certain toxic reactions, notably nausea, vomiting, hematuria, have followed its use, we believe that more extended clinical trial of this drug is justified.

#### SUMMARY AND CONCLUSIONS

1. A series of 135 cases of pneumococcus pneumonia treated with sulfapyridine and sodium sulfapyridine is reported.
2. A mortality rate of 11.1 per cent was found in the entire group of patients. The incidence of death among 99 non-bacteremic cases was 8 per cent; among 23 bacteremic cases, 21 per cent. No deaths occurred in the 23 Type I treated cases.
3. The toxic reactions and the effects of therapy upon the clinical course of the disease have been discussed.
4. In a group of 65 patients, in whom 250 blood concentration determinations were done, those showing mean blood levels of 6 mg. per cent or above had a more satisfactory clinical response.
5. Our experiences with the use of the soluble sodium sulfapyridine in 25 cases have been given. The value of this drug in the treatment of severely ill patients, or in those whose response to the oral preparation is poor, has been discussed.

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## EXPERIENCES IN THE TREATMENT OF LOBAR PNEUMONIA \*

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DURING the winter of 1938-39 the opportunity was presented to study the incidence of pneumococcus infection in a group of hospitals in the St. Louis area. We also observed the therapeutic effects of type specific rabbit serum and sulfapyridine in two series of cases. In this paper no attempt is being made to review the literature nor to enter into a discussion of the mode of action of sulfapyridine. We merely desire to present two series of cases, one drug treated and one treated with type specific rabbit serum so that as other similar series are reported a composite picture may evolve which eventually will be a guide in the future treatment of pneumococcus pneumonia.

The "quellung" method of typing was used. In all, 624 type determinations were made on various materials, comprised chiefly of sputum and throat swabs but including blood cultures, pleural fluids, lung punctures, pericardial fluid and synovial fluid. This method of typing pneumococci proved very satisfactory. On 10 occasions a repetition of the test was required in order to determine the type. The direct typing failed in 59 cases where mouse culture later revealed the type. Direct typing and mouse culture disagreed in only two cases. In eight cases pneumococci were present but no type could be determined. This suggests that these eight cases were of some type other than the 1 to 30 for which we tested. Many of these examinations were made on material from patients who did not suffer from pneumococcus pneumonia.

Three hundred and forty-nine determinations were made on material from patients suffering from pneumococcus pneumonia. The incidence of the types is based on the study of this group of 349 cases. The number of cases of each type and the percentage of the whole group are shown in table 1.

Through the kindness of Dr. Joseph Bredeck and Dr. Emanuel Sigoloff of the St. Louis Department of Health we have placed for comparison the incidence of types determined in a total of 851 cases of pneumonia reported

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this winter. The greater part of this series of 349 cases was, of course, included in the total of 851 cases. It is obvious from a study of the table that the small series of 349 cases represents in fairly accurate detail the incidence of the types of pneumococci in the St. Louis metropolitan area for this year.

TABLE I

Percentage of Incidence of Pneumococcus Types  
Series of 349 Cases. Compared with Health Department Survey,  
November, 1938 to July 1, 1939

Type	No. of Cases in Series	% Incidence in Series	% Incidence Health Dept.	Type	No. of Cases in Series	% Incidence in Series	% Incidence Health Dept.
I	65	18.6	16.6	XVI	7	2.0	0.58
I combined with other types	6	1.7	1.6	XVII	2	0.57	1.6
Total I	71	20.3	18.5	XVIII	2	0.57	1.6
II	10	2.8	2.8	XIX	16	4.5	3.6
III	38	10.8	12.2	XX	6	1.7	1.2
IV	15	4.2	5.2	XXI	1	0.28	0.9
V	30	8.5	6.2	XXII	6	1.7	0.7
VI	21	6.0	4.8	XXIII	4	1.1	2.2
VII	26	7.4	6.5	XXIV	—	—	0.82
VIII	24	6.8	8.3	XXV	6	1.7	1.0
IX	3	0.85	2.1	XXVI	—	—	—
X	3	0.85	0.82	XXVII	—	—	0.35
XI	2	0.57	1.6	XXVIII	4	1.1	0.35
XII	3	0.85	0.58	XXIX	7	2.0	1.5
XIII	6	1.7	1.6	XXX	—	—	—
XIV	4	1.1	2.5	Multiple type	30	8.5	9.04
XV	4	1.1	1.5	Types not determined	4	1.1	0.

In the study of this table it is interesting to note that Type I occurs most often, Type III with the next greatest frequency, followed by Type V. Types VII, VIII, VI, XIX, IV and II follow in the order mentioned. In four cases where there was a definite pneumonia a pneumococcus was found, but the type could not be determined. In 30 cases or in 8.5 per cent multiple types occurred. Six of these, however, were combined with a Type I organism. We observed no cases of pneumonia due to pneumococci of Types XXIV, XXVI, XXVII or XXX.

So far as therapy is concerned, this group of 349 cases of pneumonia is further divided as follows: One hundred and twenty-six cases were treated with type specific rabbit anti-serum. The types comprising this group were Types I, II, V, VII, VIII and XIV. One hundred and six cases were treated with sulfapyridine. Thirty-two cases were treated with an experimental rabbit serum which in the laboratory animal had suggested the possibility of having some "broad coverage" properties. In 85 cases not treated by the serum or the drug, the diagnosis of pulmonary involvement was verified by roentgen-ray of the lung. These cases were chiefly patients who had a definite pulmonary involvement but who were suffering in such

mild degree that no specific therapy seemed to be indicated. No deaths occurred in this group. As a rule, however, it is best to treat any case specifically as soon as the diagnosis is made, regardless of the seemingly mild clinical appearance of the infection.

#### TYPE SPECIFIC RABBIT SERUM TREATED CASES

Among the 126 cases treated with type specific rabbit serum there were 10 deaths, giving a gross mortality rate of 7.9 per cent. In the detailed study of this group which follows, five cases were not included since they died under 24 hours after serum was given.

TABLE II  
Cases not Included; Died on Day Admitted

<i>Type I</i>	
F-66—	8th day—3 lobes—bacteremia—given 400,000 Units—died 20 hrs. (SSS neg.)
M-63—	10th day—RML—empyema—bacteremia—given 140,000 Units—died 12 hrs. (SSS neg.)
F-49—	5th day—LLL—diabetic coma—bacteremia—given 140,000 Units—died 20 hrs. (no SSS)
<i>Type V</i>	
F-5—	6th day—LUL—LLL—empyema—bacteremia—given 140,000 Units—died 8 hrs. (SSS neg.)
<i>Type VIII</i>	
M-60—	8th day—2 lobes—uremia—NPN 80—bacteremia—given 180,000 Units—died 12 hrs. (No SSS)

These five cases all revealed a bacteremia and were seen late in the disease; all but one had serious complications. In three of the five deaths, the polysaccharide skin test was negative at the time of death and in two cases, the polysaccharide skin test had not yet been done at the time of death. None of these cases showed a sudden drop in blood pressure or other evidence of an immediate reaction which could have been caused by the serum administration, and so might have contributed to their sudden deaths. Since it was our feeling that these cases had not been treated adequately, we have eliminated them from the detailed analysis.

Thus we may consider a series of 121 cases of pneumonia treated with type specific rabbit anti-serum with five deaths giving a mortality rate of 4.13 per cent.

Table 3 shows this series analyzed as to type incidence, the incidence of bacteremia occurring in each type, the number of patients who recovered, the number who died, and the individual mortality rates for the various types. As is to be expected, the five deaths which occurred were all in cases with bacteremia; on the other hand, there were 14 other patients with bacteremia who recovered.

TABLE III  
121 Pneumonia Cases—Treated with Type Specific Rabbit Antiserum  
Type and Incidence—Bacteremia—Mortality Rate

Type	Total Cases	Bacteremia	No. Recovered	No. Died	Mortality Rate
I	59	8	57	2	3.38
II	13	2	12	1	7.1
V	15	5	13	2	13.3
VII	13	2	13	0	0.
VIII	19	2	19	0	0.
XIV	2	0	2	0	0.
	121	19	116	5	4.13 per cent

Table 4 is an attempt to analyze the series by separating the cases which were seen early enough in the disease to receive what was considered to be adequate treatment from those cases which were first seen after four days. Since none of the patients died who were seen before the sixth day, it is fair to state that no patients treated on the fifth day or sooner died, whereas five deaths occurred in patients who had received their first serum, two on the sixth, and one on the eighth, fourteenth and twenty-first days, respectively.

TABLE IV  
Relationship—Day of Disease—Serum First Given—Mortality

Type	Serum first given within 96 hrs. of onset			Serum given 96 hrs. or later after onset		
	No. Cases	No. Recovered	No. Died	No. Cases	No. Recovered	No. Died
I	38	38	0	21	19	2 { 6th day 14th day
II	9	9	0	4	3	1 { 8th day
V	6	6	0	9	7	2 { 6th day 21st day
VII	9	9	0	4	4	0
VIII	11	11	0	8	8	0
XIV	2	2	0	0	0	0
Total	75	75	0	46	41	5

Table 5 shows the relationship between the type of the organism and age of the patient and deaths. In agreement with many previous studies it was found that the deaths all occurred in patients 40 years of age or over.

TABLE V  
Relationship—Type—Age—Deaths—Serum Treated Cases

Type	Under 40 yrs.			Over 40 yrs.		
	Recovered	Died		Recovered	Died	
I	39	39	0	20	18	2 { 57 yrs. 63 yrs.
II	9	9	0	4	3	1 { 50 yrs.
V	8	8	0	7	5	2 { 64 yrs. 40 yrs.
VII	8	8	0	5	5	0
VIII	9	9	0	10	10	0
XIV	2	2	0	0	0	0
Total	75	75	0	46	41	5

Of the 116 who recovered, 94 or 81 per cent displayed a crisis (normal temperature within 24 hour period after administration of serum). Twenty-two or 19 per cent recovered by lysis (temperature falling to normal within a period of 48 hours or longer).

Table 6 shows the incidence and extent of the immediate reaction to the administration of rabbit serum. We observed a sharp reaction in three patients, two of whom recovered. Since the other patient who ultimately died lived for 14 days following the administration of the serum, it is our feeling that death could not be attributed to shock or serum administration. This patient at autopsy showed a complicating endocarditis with vegetations on the aortic valve and was also a chronic alcoholic; he had received 280,000 units of serum.

TABLE VI  
Incidence of Immediate Reaction to Intravenous Rabbit Serum

Type	Recovered			Died			Total Cases	Total Reactions
	Mild	Moderate	Severe	Mild	Moderate	Severe		
I	19	7	1	1	0	1 (lived 14 days)	59	29
II	2	2	1	0	0	0	13	5
V	7	3	0	0	1 (lived 7 days)	0	15	11
VII	2	2	0	0	0	0	13	4
VIII	5	1	0	—	—	—	19	6
XIV	1	0	0	—	—	—	2	1
Total	36	15	2	1	1	1	121	56 or 46.2 %

Mild—37 or 30.5%      Moderate—16 or 13.2%      Severe—3 or 2.4%  
Mild—chill—less than 1° temp.      Moderate—chill—more than 1° temp.      Severe—shock.

Table 7 shows the incidence of serum sickness in the 116 patients who recovered. By "mild" it is meant that the patient had scattered urticaria. By "moderate" we indicate urticaria and one to two degrees of fever with joint pains lasting not more than 48 hours. By "severe" we indicate those who had more severe urticaria combined also with fever and swelling of the joints, the duration of which was more than 48 hours.

It is interesting to note that the total incidence of 25.8 per cent serum sickness is considerably lower than the incidence formerly associated with the administration of horse serum.

It would appear that there was some factor in the type specific serum for types V and VII which tended to cause these severe reactions as none occurred with the use of Types I, II, VIII, and XIV serum. All of the sera were adequately tested for thermal reactions before being used clinically and were found satisfactory.

TABLE VII  
Incidence Serum Sickness—116 Patients Who Recovered

Type	Total No. of Cases	Mild Reaction	Moderate Reaction	Severe Reaction
I	57	10	5	0
II	12	1	0	0
V	13	2	1	2
VII	13	2	0	3
VIII	19	4	0	0
XIV	2	0	0	0
Total	116	19	6	5

Total of 30 cases of serum sickness—incidence 25.8 per cent.

#### TECHNIC OF SERUM ADMINISTRATION

After typing of the sputum which was obtained after the patient had washed the mouth thoroughly with normal saline solution, the tests for sensitivity to rabbit serum were performed. One-tenth c.c. of a 1:100 or a 1:10 dilution of normal rabbit serum in physiological saline was injected intracutaneously on the forearm and one drop placed in the conjunctival space of one eye. The absence of conjunctivitis was noted before this was done, and a careful history regarding allergy or previous serum administration was obtained. Epinephrine 1:1000 in a hypodermic syringe was ready for use before the tests were done. If the tests were negative after 15 minutes, 1 c.c. of a 1:10 dilution of the therapeutic serum was given intravenously, slowly, over a period of five minutes. The blood pressure and pulse were noted before and five minutes after this was given, and the blood pressure cuff was left in place to facilitate readings every few minutes during the next hour. If there was no reaction or fall in blood pressure exceeding 20 mm. mercury, the balance of the serum was then given slowly by the gravity method, allowing at least one hour for 100 c.c. of serum, which amounted in most instances to 100,000 units.

If a drop in blood pressure of more than 20 mm. Hg occurred, or if the patient had any increase in respiratory difficulty and/or pulse rate increase of more than 30 beats per minute, the injection was stopped and epinephrine was given. Although a significant drop in blood pressure occurred in several cases, it was possible to continue the administration of serum cautiously after a few minutes' interval. Only in the presence of hives or severe respiratory distress and fall in blood pressure was epinephrine necessary. In many cases aspirin was given before the serum. It was felt that perhaps the aspirin decreased the severity but did not affect the incidence of chill and thermal reactions. No controlled study was made of the effect of aspirin. There was no appreciable difference in reaction or therapeutic efficiency in cases where the serum was given diluted with 200 c.c. of normal saline or when given in concentrated form.

Table 8 indicates the amount of serum administered in the group of cases.

The total is being presented merely to show the relatively small dosage used as compared with recent recommendations. It is our belief that the use of the type specific polysaccharide skin test which was used routinely in all the serum treated cases enabled us to gauge the optimum dosage of serum therapy, thus effecting a considerable saving of serum. The application of the polysaccharide skin test in this respect is more fully discussed in another report, which has been accepted for publication in the Journal of the American Medical Association.

TABLE VIII  
Pneumonia Cases Treated—Specific Rabbit Antiserum  
Amount of Serum Administered—Number of Doses

Type	Average Amount—Units	Limits—Units	Average No. Doses	Limits
I	116,000	40,000–280,000	1.6	1–6
II	160,000	120,000–340,000	1.8	1–6
V	160,000	100,000–360,000	2.0	1–6
VII	125,000	80,000–220,000	1.5	1–3
VIII	117,000	60,000–220,000	1.3	1–3
XIV	90,000	80,000–100,000	2.0	1–3

No figures are being presented as to the length of stay in the hospital because the different economic conditions encountered made such figures worthless. The well-to-do patients could go home early and receive adequate care, or stay longer with special nursing as they desired. The poor patients were kept in the hospital only as long as necessary.

#### INCIDENCE OF COMPLICATIONS

In this series of 121 cases the complications due to pneumococcus invasion elsewhere than the lungs consisted of 12 cases of empyema; 9 type I; 1 type II; 2 type V. Of these, one patient of the type I group died. There was one case complicated by otitis media occurring in the type I group, with complete recovery. There were two cases of endocarditis, both of whom died. One occurred in the type I group and one occurred in the type V group. The type V case also had empyema which was not included in the 12 cases of empyema recorded above. Four of the five deaths in the total series were in cases presenting complications.

#### SULFAPYRIDINE TREATED CASES

The series of 143 cases of pneumonia comprised 106 noted previously in this report in the discussion of the general type incidence of pneumococcus pneumonia and 37 additional untyped cases of pneumonia proved by clinical signs and roentgen-ray of the chest. The majority of these 37 cases were in infants and children; smears had shown the presence of pneumococci in all but six. Pneumonia in these six cases may have been due to organisms or virus other than pneumococcus but since no deaths occurred among the six, they are included in the series. The one death listed in this group of 37

cases was in an elderly man of 79 years with myocarditis, and autopsy showed pneumococci by smears but cultures were not done.

In the series of 143 there were 13 deaths giving a gross mortality rate of 9.09 per cent. One case is not included in the detailed study below as she was admitted in a moribund state and died shortly after admission. This patient was a female 60 years of age, admitted on the sixth day of disease with left lower lobe involvement. Later information revealed that she had a bacteremia with a Type III pneumococcus. She was given 4 grams of sulfapyridine but died within six hours.

TABLE IX  
Sulfapyridine Treated Cases—Type Incidence—Mortality Rate

Type	No. Cases	Bacteremia	Recovered	Died	Mortality Rate
I	8	0	8	0	0.0
II	1	0	1	0	0.0
III	25	3 (1 recovered	21	4	16.0
IV	8	0	8	0	0.0
V	8	1 (died)	7	1	12.5
VI	7	0	6	1	14.3
VII	4	0	3	1	25.0
VIII	6	0	5	1	16.6
IX	2	0	2	0	0.0
X	1	0	1	0	0.0
XI	1	0	1	0	0.0
XII	1	0	0	1	100.0
XIII	1	0	0	1	100.0
XIV	3	0	3	0	0.0
XV	1	0	1	0	0.0
XVI	3	0	3	0	0.0
XVII	2	0	2	0	0.0
XVIII	2	1 (died)	1	1	50.0
XIX	8	0	8	0	0.0
XX	0	0	0	0	0.0
XXI	1	0	1	0	0.0
XXII	0	0	0	0	0.0
XXIII	0	0	0	0	0.0
XXIV	0	0	0	0	0.0
XXV	2	0	2	0	0.0
XXVI	0	0	0	0	0.0
XXVII	0	0	0	0	0.0
XXVIII	0	0	0	0	0.0
XXIX	2	0	2	0	0.0
XXX	0	0	0	0	0.0
Multiple					
I+VIII	1	0	1	0	0.0
X+XXI	1	0	1	0	0.0
XX+XIV	1	0	1	0	0.0
II+XVI	1	0	1	0	0.0
I+XV	1	0	1	0	0.0
III+VIII	1	0	1	0	0.0
XV+XXIII	1	0	1	0	0.0
Total typed	105	5	94	11	
Not typed	37	0	36	1	
TOTAL	142	5	130	12	8.4%

The remaining series of 142 cases of pneumococcus pneumonia treated by sulfapyridine is analyzed as follows:

Table 9 shows the type incidence combined with the incidence of bacteremia and the mortality rate. The significant points are the relatively large number of cases of Type III, there being 25 such cases with three instances of bacteremia and four deaths. Two of the deaths were in bacteremia cases and two of the cases which died did not show bacteremia. This gives a mortality rate of Type III cases treated by sulfapyridine of 16 per cent, which is comparable to other reports. It is also interesting to note that in this group there were seven cases where multiple types occurred but where there were no deaths.

Table 10 shows the relationship of age groups of patients; the bacteremia incidence and the mortality rate. There were three deaths in the age group under two years; one of these deaths was in a girl three months of age with a pneumonia of Type XIII with complicating pyo-pneumothorax and bilateral otitis media. This patient had not been seen before the fifth day of the disease. The second patient was a child just under two years with a Type V pneumonia and a positive blood culture, seen first on the sixth day of disease. The third case was a three weeks old infant in which no typing was secured. Treatment was instituted after the fourth day of disease with death on the third day of drug therapy. There were no deaths in the age group between 2 and 40 years of age. There was a total mortality rate of 8.4 per cent. A significant point is that in this group 98 cases were treated within five days of onset and thus, theoretically, received adequate treatment; nevertheless two of these patients died. The majority of deaths occurred in patients seen for the first time on the fifth day or later.

TABLE X  
Sulfapyridine Treated Cases—Age—Day of Disease—Mortality Rate

Age	No. Cases	Bacteremia	Recovered	Died	Mortality Rate
0-2	27	0	24	3	7.3
2-10	26	1	26	0	0.0
11-20	18	0	18	0	0.0
21-30	8	0	8	0	0.0
31-40	17	0	17	0	0.0
41-50	9	1 (died)	8	1	11.1
51-60	13	2 (died)	9	4	30.9
61-70	13	1	13	0	0.0
71-	11	0	7	4	36.3
Total	142	5	130	12	8.4%

Treated within 96 hrs. —98 cases—2 deaths  
Treated later than 96 hrs.—44 cases—10 deaths

#### INCIDENCE OF COMPLICATIONS

Of the 142 cases treated with sulfapyridine, eight had complications caused by pneumococci. Four were empyema; four were otitis media. There was one death among the four with empyema. Three cases had arteriosclerotic heart disease with decompensation; one of these died. An-

other patient who died had periods of auricular fibrillation. There were seven patients who had more than one type of pneumococcus in the sputum, none of whom died.

#### ADMINISTRATION OF SULFAPYRIDINE

Sulfapyridine was given according to age and weight of the patient. In general, however, all adults without renal or hepatic complications were given 1 gram every hour for the first four hours, then 1 gram every four hours night and day until the temperature had remained normal or not above 100.5° F., or 38° C. for at least two days. Rarely was it necessary to exceed a total of 30 grams for adults.

We gave 0.15 gram every four hours to infants under three months of age; 0.3 gram to those six months to one year of age; and the same every three hours to those one to two years old; 0.6 gram every four hours for five year olds and 0.9 gram every four hours in the 12 year age group. The rule of giving 0.1 gram per kilo of body weight may result in too small a dose for children and infants. Crushing the tablets and administering them in a mixture of apple sauce, syrup or in gelatin capsules is useful at times.

The daily dose necessary to effect a concentration of 5 to 10 mg. per cent varies for different individuals. There is a marked variability in the absorption of the drug in different persons. The above level was found satisfactory but the effective level, as judged by the concentration in the blood, varies.

The precaution observed in the use of sulfanilamide, of not simultaneously giving magnesium sulfate, was likewise exercised here. Very seldom was it necessary to give methylene blue, but when given, the intravenous route was used because it seemed to cause less nausea than the oral administration.

Attention should be called to the need for careful observation of the blood counts, and of the urine, both during and several days after administering sulfapyridine. If gross hematuria, "stones" of sulfapyridine or severe decrease in number of blood cells of either variety, occurs, sulfapyridine should be discontinued and liberal amounts of fluid given by mouth or as 5 per cent glucose in saline by vein.

#### TOXIC MANIFESTATIONS

Two patients had "drug fever," one of these had a rash which disappeared when the drug was discontinued. There were three cases exhibiting a patchy erythema due to sulfapyridine. The occurrence of microscopic hematuria was rather frequent. No cases of gross hematuria were seen and no cases of proved renal calculi, due to sulfapyridine, were observed. It may be significant that no attempt was made to concentrate the drug in the serum by limiting fluid, but on the other hand, fluids were forced to a total of 3 to 5 liters per day in all drug treated cases. Due to the fact that in

two cases the plasma non-protein nitrogen rose after sulfapyridine therapy, the drug was not used in elderly patients showing evidence of marked renal damage. One case of Friedlander's pneumonia (not included in the series) developed jaundice one month subsequent to three weeks of sulfapyridine therapy (6 grams daily for two weeks and 3 grams daily for one week). All gastrointestinal and genito-urinary and gall bladder examinations were negative. Recovery from the jaundice was slow but complete.

In two patients of this series the erythrocyte count dropped by 1,000,000 cells in 24 hours, so the drug was discontinued. The patients recovered. There was no jaundice or untoward reaction. No case of agranulocytosis was encountered. In 48 per cent of the patients nausea and vomiting incident to the administration of sulfapyridine occurred. If the vomiting became too severe and interfered with nutrition the drug was discontinued, or in a few cases the sodium salt was given by rectum. Many times the administration of the drug, crushed and mixed with food or placed in capsules was followed by improvement in the nausea. The parenteral use of normal saline solution did not help the nausea greatly. Others have found the use of oxygen inhalation, especially 100 per cent oxygen, helpful in relieving nausea due to sulfapyridine.

Of the 130 drug treated cases that recovered the temperature dropped to normal in 74 patients within 24 hours and in 93 of the patients the temperature was normal within 48 hours.

#### DISCUSSION

Due to a number of factors the serum treated series and the drug treated series are not comparable. No Type III patients received serum. There was a much larger percentage of infants and young people in the drug treated cases than in the serum treated cases. The series of drug treated cases contained a relatively small number of Types I, II, V, VII, VIII and XIV. Certain points, however, seem to be significant: (1) In the serum treated cases there were no deaths in the small groups of Types VII and VIII although the percentage of bacteremia in these groups was 15.3 per cent for Type VII and 5.2 per cent for Type VIII. In the drug treated cases there was one death each in Type VII and in Type VIII, neither of which disclosed a bacteremia. (2) In both series the highest mortality rate was in the individuals over 40 years with the secondary peak of mortality in the drug treated cases in those under two years of age. (3) In the serum treated series there were no deaths among the patients seen for the first time before the fifth day. In the drug treated series there were two deaths when the patients were seen early enough in the disease to receive, theoretically, adequate treatment. (4) Ninety-four or 81 per cent of the 116 serum treated cases recovered by prompt crisis, whereas, only 74 of the 130 patients, or 56.9 per cent of those who recovered in the drug treated group had a drop in temperature to normal within 24 hours. Pertinent in this connection is

the observation that after the crisis in the serum treated cases, the patient was practically well, clinically, whereas in the drug treated cases the patient was still very sick for several days after defervescence of temperature and frequently required continuous administration of oxygen.

Although an effort was made to maintain a blood concentration of 5 to 10 mg. per cent of the drug, it is interesting to note that the majority of the patients who recovered did so within the first 24 to 48 hours with the concentration in the blood varying between 2 to 16 mg. per cent in different cases.

#### CONCLUSIONS

1. The specific rabbit anti-pneumococcus serum appears to be a very effective form of treatment for pneumonia caused by pneumococci of Types I, II, V, VII, VIII and XIV.
2. Sulfapyridine is of great value in the treatment of pneumococcal pneumonia, and, particularly with the Type III organism against which specific serum therapy has not been markedly effective.
3. Sulfapyridine is of value in the treatment of pneumococcal pneumonia where for one reason or another typing cannot be performed or where type specific serum cannot be secured. It is also of value in selected cases when combined with serum therapy.
4. Regardless of the method of treatment, the age group of the patients bears a very definite relationship to the mortality rate.
5. Regardless of the method of treatment, the day of disease upon which treatment is instituted bears a very definite relationship to the mortality rate.

## STUDIES IN PERIPHERAL VASCULAR DISEASE

### I. INTRAVENOUS CALCIUM IN OCCLUSIVE VASCULAR DISEASE\*

By H. S. WEICHSEL, M.D., *New York, N. Y.*

THE use of calcium in obliterative vascular diseases is not a radically new departure. Its use in these conditions, by the venous route, has not to my knowledge been previously reported. Bernheim and London<sup>4</sup> have administered calcium orally in some cases and have reported some success in spastic conditions. The mode of action has, however, not been adequately explained.

In order to reduce to a minimum the amount of fluid used in saline therapy of obliterative arterial diseases, calcium gluconate was employed, in 10 per cent solution, in amounts of either 10 or 20 cubic centimeters. This was substituted for the 300 cubic centimeters of 5 per cent sodium chloride solution commonly used in some clinics for peripheral arterial disease. The idea was to find out, if possible, whether a salt, per se, exercised the main effect or whether a relatively large amount of fluid played any important part in the results obtained. A report on this point will be made in the near future.

Calcium salts were injected intravenously in a number of cases. In 30 of these recordings were made, with the Tycos recording oscillometer, of pulse amplitude before and after injection. In other cases, observations were made with the Pachon-Boullite oscillometer. Both instruments showed an appreciable augmentation of the pulse amplitude in a considerable number of cases.

The most striking phenomena, however, were clinical. Most noteworthy were relief from pain and increased ability on the part of the patients to walk. This needed explanation.

Following the intravenous injection of calcium salts, there is a generalized flush and sensation of heat, starting usually in the throat, and spreading gradually all over the body. This occurs in normal persons as well as in those with impaired peripheral circulation. No rise in blood pressure is observed. With considerable constancy, a drop is noted in both systolic and diastolic levels, more marked in the diastolic as a rule. This fall in blood pressure has also been observed by others.<sup>9, 20, 28, 80</sup> There is also, quite constantly, a slowing of the pulse rate. Nausea occurs occasionally. The extreme thirst which follows infusion of hypertonic saline solutions is not

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present after calcium injections. This would indicate that tissue fluids are not suddenly withdrawn from the tissues in order to dilute to isotonicity the excess salt, thereby rapidly increasing the blood volume. If the blood volume is not increased, how are we to account for what seems to be increased circulation? There must be some specific action of the calcium ion, and this action would seem to be essentially vasodilator.

Little has been written concerning the action of calcium on blood vessels. There is considerable published work on the cardiac action which has been admirably summarized by Berliner.<sup>2</sup> There is some disagreement, but the bulk of evidence seems to bear out the contention that calcium acts as a vasodilator. The effect of calcium on the autonomic nervous system is also not yet finally established. The effect of calcium on smooth muscle has been observed to be antispasmodic. These three factors evidently play some part in the mechanism of the findings previously mentioned. Which action is dominant, or what their interrelation may be, is not yet clear. Let us evaluate them separately and then try to correlate them in regard to their concerted action *in vivo*.

The general flush and the feeling of warmth after the infusion of calcium salts lead one to believe that superficial vessels are being dilated. How else does the skin become red and hot? This impression is strengthened by the sensation of heat in an extremity which had previously been cold for months or years because of deficient circulation. This view is shared by Sollman,<sup>35</sup> Zondek,<sup>43</sup> and Hunter.<sup>17</sup> Major and Stephenson<sup>24</sup> point out that the administration of calcium salts reduces the hypertension induced by methylguanidin. They ascribe a vasodilator action to calcium. Mancke<sup>25</sup> explains increased heart action after the administration of calcium as due to coronary dilatation, with increased flow of blood to the heart muscle. Hochrein<sup>16</sup> observed the dilator action of calcium on coronary vessels even after complete denervation of the heart. Schmidt<sup>47</sup> found that perfusion with calcium salts induced a vasodilatation in the frog, cat and rat. The flow, measured by drops per minute, increased 11 to 50 per cent over the normal rate.

Figure 1 is an oscillometric record obtained in a man with long established thromboangiitis obliterans. It will be observed that pulsation before injection is small. After injection of 2 gm. of calcium gluconate, pulsation is definitely increased. Ten minutes later the pulsation is still larger, and after 20 minutes it is about three times the original amplitude. This does not mean that the actual blood flow has increased in exactly that proportion. Mechanical factors of error in the recording apparatus are, no doubt, responsible for some distortion. But the fact remains that a distinct increase in pulse amplitude is recorded.

Figure 2 is a similar record from a man well over 60, with advanced arteriosclerosis. A similar result is apparent in this instance, but to a lesser degree. This is explained by the relatively smaller development of collateral

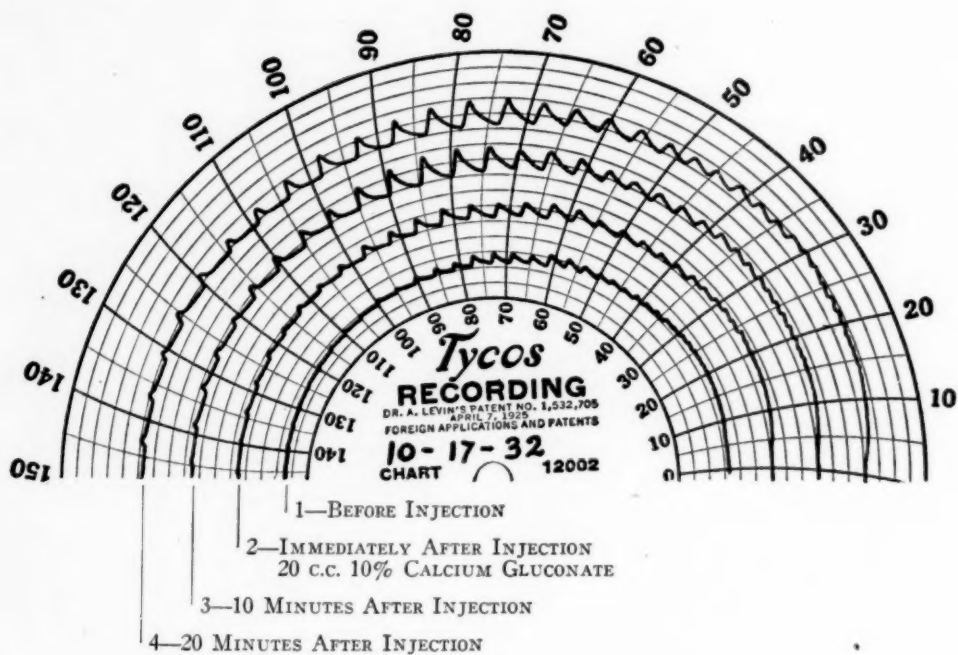


FIG. 1.

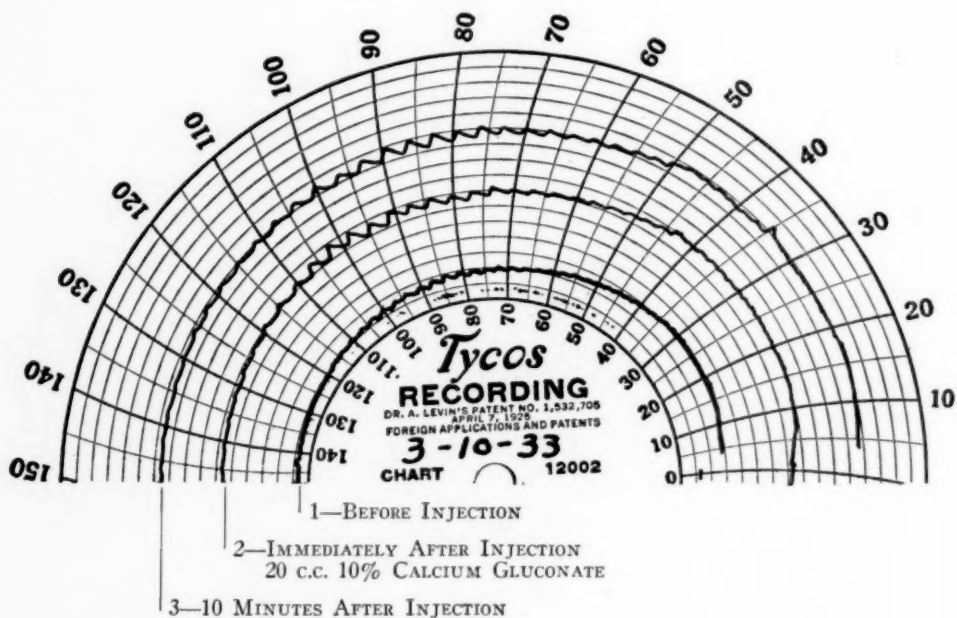


FIG. 2.

circulation in arteriosclerosis than in thromboangiitis obliterans. Of this, more later.

These records are fairly characteristic of the response regularly elicited. The others are similar. A few cases show no demonstrable evidence of this response. But, despite the absence of demonstrable evidence of increased pulse amplitude, patients get relief after injection of calcium salts. This can be explained as due to the dilatation of the collateral bed of small, nonpulsating vessels which can neither be felt nor measured but which do, in their dilated state, bring more blood to previously ischemic tissues. From the foregoing evidence, it may be presumed that calcium salts act as vasodilators.

There is some disagreement in the literature as to whether calcium stimulates the sympathetic or the parasympathetic. The observations recorded above tend to support the latter view. The analogy between calcium effects and vagus effects on heart rate and contractions is striking. Wolffe and Bellet<sup>41</sup> observed cessation of auricular paroxysmal tachycardia after administration of calcium salts. Stimulation of the vagus by various means will also stop these attacks. The inference is obvious. Billigheimer<sup>5</sup> observed that calcium stops adrenalin tachycardia immediately, but, when the tachycardia is produced by vagus paralysis with atropin, calcium has no effect. If this be so, it is logical to assume that calcium acts in this instance by vagus stimulation, a parasympathetic phenomenon. Petzetakis<sup>29</sup> also observed that calcium increases vagus irritability and that it stops extrasystoles and attacks of tachycardia. Stimulation of the vagus slows the heart. Bradycardia after infusion of calcium has been repeatedly observed by myself and by many others.<sup>8, 40, 39, 20, 9, 6, 7, 44</sup> Seekles, Sjølløma and van der Kaay<sup>33</sup> interpreted this bradycardia as a vagotonic manifestation. Edwards and Page<sup>12</sup> observed bradycardia after parathormone which induces a hypercalcemia. Hueper<sup>48</sup> observed that when parathyroid extract was given in sufficient amount to raise the blood calcium to 15 mg. per cent, marked diuresis occurred and that blood vessels, especially glomerular capillaries, were extremely distended with blood. All these facts point to a direct parasympathetic stimulation by the calcium ion or else to a parasympatheticomimetic function, through some other means, via the calcium ion. The component parts of the autonomic system being largely antagonistic, it would thus appear that calcium plays an antisympathetic rôle.

Sympathetic fibers to the extremities have been demonstrated by Kramer and Todd,<sup>19</sup> Woollard and Norrish,<sup>42</sup> Moore, Williams and Singleton.<sup>27</sup> Woollard<sup>49</sup> states: "Vasoconstriction is a continuous and tonic effect of the sympathetic system." . . . "The tonic constrictor supply by the sympathetic is the only continuous active pressor system that is known . . . something like 50 per cent of the normal blood pressure is dependent on these pressor impulses." Again: "These pressor influences pervade the entire body with the possible exceptions of the heart . . . the brain . . . and the lungs." Also: "Vasodilators include some special nerves, the chorda tympani, the cranial

parasympathetic in general, the pelvic nerves, the sacral parasympathetic . . . and finally, there is some evidence in most parts of the body of some vasodilators which belong to the gray rami of the sympathetic. These, however, are overshadowed by the vasoconstrictor fibers present in these same rami." Finally, the reports, too numerous to mention, of the results of sympathetic ganglionectomy, bear out the vasoconstrictor effect of the sympathetic system.

This leads logically to the question: "Could not the calcium effect in this instance be the result of inhibition of the neuromuscular junction between the sympathetic fibers and the smooth muscle of the arterial wall?" The inhibitory action of calcium on neuromuscular junctions has been observed by many.<sup>43, 5, 29, 37, 38, 17, 24</sup> If this action is unselectively applicable to all neuromuscular junctions, without specific predilection for any particular group or type of fibers, the matter readily resolves itself into a quantitative determination of the number of sympathetic and parasympathetic fibers in any given area. Since at least the preponderant innervation of blood vessels is sympathetic-constrictor, an inhibitory effect on these nerve endings should produce vasodilatation.

The antispasmodic action of calcium on smooth muscle is well known. Bauer, Salter and Aub<sup>1</sup> find that infusion of calcium immediately relieves the pain of biliary and ureteral colic. Sollman<sup>36</sup> describes the arrest of intestinal peristalsis as one of the toxic effects of intravenous calcium administration. The antispasmodic effect of calcium in lead colic has also been observed by Hunter.<sup>17</sup> Kennedy<sup>18</sup> gives experimental evidence to prove that calcium excess in perfusing fluid causes a loss of tone in smooth muscle. Now, since the tonic pressor innervation of the arterial smooth muscle is preponderantly sympathetic, these facts seem further to prove the antisymphathetic action of calcium.

If the vasodilator function of calcium is accepted, its value as a therapeutic agent in occlusive vascular disease is still open to question. It is not rational to believe that any substance can actually dilate an occluded vessel. The important consideration is the effect on the collateral circulation. Buerger<sup>10</sup> has called attention to the formation of collaterals in thromboangiitis obliterans. Meleney and Miller<sup>20</sup> and Lewis and Reichert<sup>21</sup> have demonstrated arteriographically that the collateral development in thromboangiitis is much greater than in arteriosclerosis. The problem involved in treating peripheral vascular occlusions is to foster the development of collateral circulation adequate to maintain nutrition of the parts more rapidly than the occlusive process can extend. By this means, the clinical condition should improve, or should, at the very least, get no worse. Clinical improvement has, so far, indicated the usefulness of calcium salts for this purpose.

Lieberman<sup>23</sup> warns of intravascular thrombosis after injection of calcium. He used toxic doses, much larger proportionately than can be tolerated in treatment. Two grams of a calcium salt is not a toxic dose, prop-

erly given. I have not seen either thrombosis or severe toxic response in many thousands of injections, other than the flush or a slight nausea.

Clinically, the salient results have been relief from pain and increased ability to walk. At first, relief from pain lasts about 24 hours, later becoming semipermanent as treatment is continued. Night cramps and rest pain have been consistently relieved. Previously cold extremities become warm again. Patients generally return of their own volition for treatment after the first course is over. They soon get to know when they need further help. It is not uncommon for patients to remain relieved for as much as two years at a time.

Earlier in this work, calcium gluconate was used. Ten or 20 c.c. (one or two grams) of a 10 per cent solution were injected slowly enough to produce only a mild flush. Rapid injection causes unpleasantly great heat, bradycardia and nausea. Very rapid injection may cause syncope. Haste is not advisable. Since this syringe technic is tedious, and because of the relative expense and instability of the older gluconate solutions, calcium chloride (diluted to about 1 or 2 per cent to prevent intravascular irritation) was tried with very satisfactory results.

The method now used is to add to an infusion of normal saline the required amount of a 50 per cent stock sterile solution of calcium chloride. This is done after the injection is started with the normal saline to be sure that venepuncture is clean. A 300 c.c. Pyrex salvarsan tube is used, and glass Luer slip connectors show by reflux of blood when the vein has been entered. The method is cheap, safe, easy to use, and offers fair protection against perivenous infiltrations due to faulty vein puncture. The few infiltrations that have occurred have not caused any appreciable damage or discomfort. The method is so simple as to be available to the bed-patient at home as well as in hospital or office.

Because of the synergism of calcium and digitalis, no digitalized patient should ever get calcium. Death may result. Berliner<sup>2</sup> and Gold and Kwit<sup>50</sup> have commented on this aspect. It is, therefore, a rule never to accept for treatment any patient receiving digitalis. All other sources of medication are carefully investigated in order to prevent errors and possible fatalities.

For the sake of brevity, results are tabulated in the following tables. No cases of short duration are presented. Most of the cases are arteriosclerotics. All patients received two grams of calcium chloride once a week for 12-week periods. The figures indicate distance walked over level ground before claudication set in, measured by patients themselves.

Figure 3 shows claudication distances before and after treatment. Original claudication distances, one-half to five blocks, are indicated by blank spaces. Dark spaces indicate improvement over and above original distances.

Figure 4 shows the degree of improvement. Percentage improvement is obtained by adding two ciphers to the figures. All original distances were reduced to a common denominator, the blank space. Improvement is in-

licated by the dark spaces. The three high figures, 40, 52 and 60, may seem fantastic but are definitely not. They are an actual index of regular ability to walk after sufficient treatment in the respective cases. The usual run of cases shows improvement not over 10 or 12 times the original claudication distance.

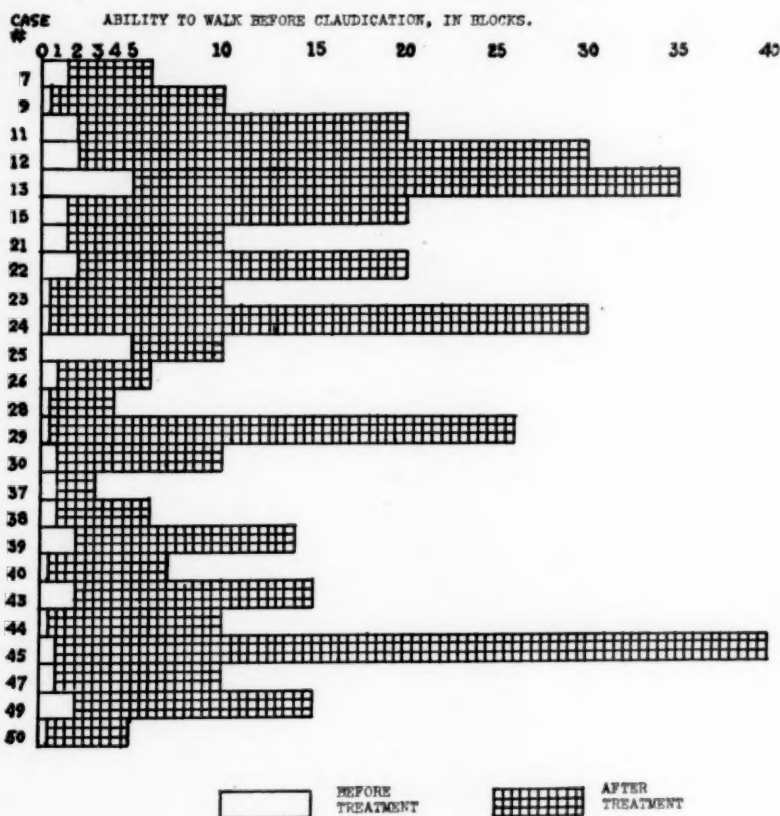


FIG. 3. Claudication distance.

Several patients showed consistent improvement in spite of gradual reduction in oscillometric readings over a period of years. This would indicate a good rate of augmentation of the collateral circulation.

#### SUMMARY AND CONCLUSIONS

It appears that the intravenous use of calcium salts, in suitable and adequate dosage, is of value in peripheral occlusive arterial diseases. The calcium effect seems to be vasodilator, on a parasympathetic or antisymphathetic basis. Claudication distance has been materially and consistently increased, rest pain and night cramps have been reduced, and ulcers have been healed with this therapy alone.

Calcium and digitalis therapy must never be mixed.

This report does not announce a panacea, nor does it in any way minimize the value of other therapeutic modalities. Rather, a form of treatment is

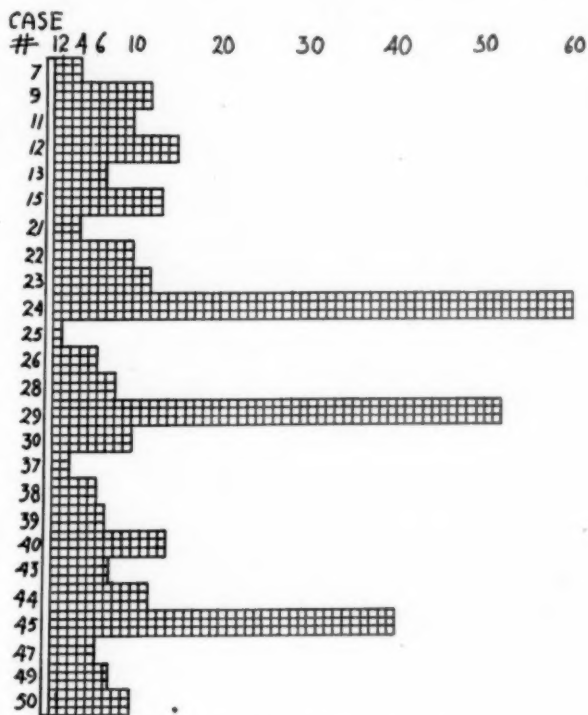


FIG. 4. Degree of improvement.

presented which is safe, cheap, simple and evidently effective. Coupling this therapy with other modalities has been found effective. It is hoped that other investigators may find the opportunity to check the method in a sufficient number of cases adequately to evaluate it.

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## INDEPENDENT VS. INTERCONNECTED TIME MARKING SYSTEM EMPLOYED IN ELECTROCARDIOGRAPHS \*

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### INTRODUCTION

IN spite of the fact that the electrocardiograph long ago attained its majority, there still appears to be a considerable amount of misunderstanding in the minds of physicians, including many who have had years of experience in the field of electrocardiography, as to what constitutes a reliable and accurate time marking system.

In interpreting an electrocardiogram, if any thought at all is given to the matter, it is usually considered that if the time marks on the tracing are uniformly and evenly spaced, they must be correct, and conversely, if they are not even or uniform in their spacing, or if their spacing varies from time to time, they are incorrect.

In many cases, the reverse is the case. An accurate time marker, entirely independent of the mechanism which drives the paper or films, will produce time marks which are entirely accurate, even though variations in the speed of the paper or film cause the spacing between the time marks to be uneven. These time intervals can be measured and interpreted with perfect confidence in their accuracy.

Conversely the non-independent "time" marker, driven from the same mechanism which drives the paper or film, will always produce "time" lines which are uniformly and evenly spaced, regardless of variations in the speed of the paper driving mechanism, and consequently of the paper. Such time marks always *look* correct, although they may be considerably in error. A prolonged P. R. interval, or an apparent arrhythmia may be due to nothing more than a variation in the speed of movement of the paper or film.

*Figure 1.* Rate—113 per minute. Tracing taken with a portable electrocardiograph which has an interconnected time marking system. The patient's clinical heart rate was 96 per minute while the tracing indicates the heart rate to be 113 per minute and a sinus arrhythmia which was not present clinically.

*Figure 1-A.* This tracing was taken of the same individual as figure 1, while deliberately varying the camera speed. The heart rate appears to vary from 112 to 150 per minute and the sinus arrhythmia is quite marked. In spite of the fact that the mechanical factors are responsible for this inaccuracy, the timing device fails to show it. The dark area in this tracing also

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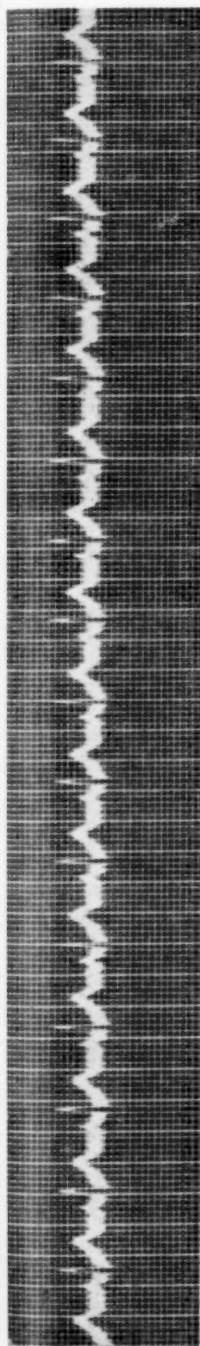


FIG. 1.

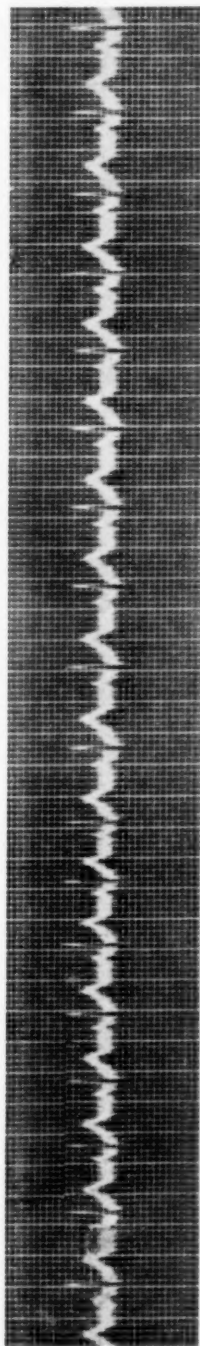


FIG. 1-A.

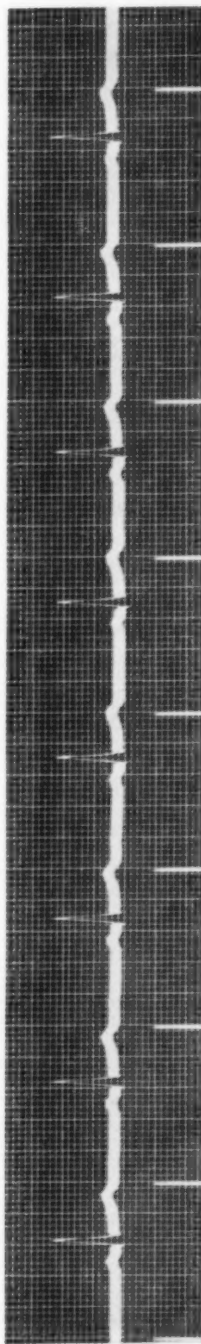


FIG. 2.

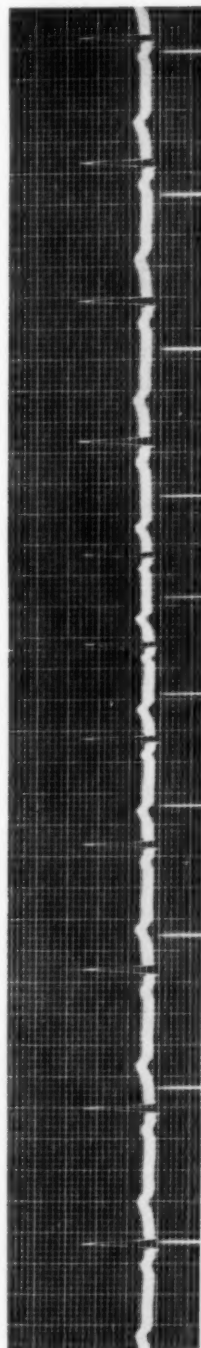


FIG. 2-A.

demonstrates the slowing of the camera without any change in the time marking.

A description of the characteristics of these two classes of time marker will make the foregoing clear.

#### INDEPENDENT TIME MARKER

The independent time marker is, as its name implies, one which operates entirely independently of the motor which drives the camera (photographic recorder). An independent time marker, to give any assurance of accuracy, must be so designed as to run in synchronism with a source of current which provides a series of impulses at a known and invariable rate. Such a series of impulses is obtainable from any well-controlled alternating current lighting circuit, from a well-adjusted electrically driven tuning fork, from a contact-making pendulum, or a contact-making clock.

Since, in electrocardiography, the universally accepted time intervals are represented by a series of marks on lines  $\frac{1}{25}$  or 0.04 second apart with every fifth line so accentuated as to represent  $\frac{1}{5}$  or 0.2 second, it is practically essential to employ a rotary form of time marker, as it is not possible with any non-rotary form to produce these accentuated lines every  $\frac{1}{5}$  second.

Accordingly, the most practical form of independent time marker consists of a small, low power, true synchronous motor, either of the solid iron, toothed rotor type (hand starting) or of the shaded-pole self-starting type. On the output shaft is mounted a wheel with five spokes, one spoke being wider than the other four. These spokes intercept the light beam which is projected by the galvanometer into the photographic recorder, each spoke, as it passes through the beam, cutting off the light, and producing a thin line across the moving strip of bromide paper or film, during the momentary dark period. The fifth extra wide spoke causes a dark period of longer duration, producing a heavier or thicker line.

By the correct choice of the number of rotor teeth in the solid iron rotor type, and the correct choice of reduction gearing in the shaded pole self-starting type, both types may be driven by, and in synchronism with, either an electrically driven tuning fork, or a commercial frequency alternating current.

Independent time markers of this nature are positive in their accuracy. The time marks which they produce in the photographic record are absolutely correct, no matter how the speed of the moving paper or film may vary.

#### NON-INDEPENDENT TIME MARKERS

A time marker is non-independent when it is interconnected with, and driven by the same source of power which drives the photographic recorder. Such time markers are still incorporated in certain types of electrocardiographs. These machines are adequate in the hands of the experienced, particularly if they have facilities to check any questionable electrocardiogram.

The main reasons for their use are: first, their cheapness; second, in the case of vacuum tube electrocardiographs, that the introduction of any device, in close proximity to the amplifier, which operates either from alternating or from intermittent direct current, will, almost inevitably, produce an objectionable amount of electrical interference in the record.

It should be perfectly obvious that in the case of a "time marker" geared to, and driven by, the same mechanism which drives the paper or film, any variation in the speed of the driving mechanism, and, in consequence, of the paper or film, must be accompanied by a corresponding and absolutely proportional variation in the speed of rotation of the "time" wheel and, consequently, the "time" marks on the tracing will *always* be exactly the same distance apart, regardless of the speed of the paper or film.

To put it another way, an interconnected "time marker" will always produce a time mark each time the paper or film has moved a definite distance. Therefore, if the time marker is so geared as to produce "time" marks one millimeter apart, which is the usual practice, these marks will always be one millimeter apart, regardless of speed, or variation in speed, of the paper or film, and regardless of the *time* required to move the paper or film a distance of one millimeter.

Once this is clearly understood, it must be equally clear that such a non-independent "time marker" is not a true time marker, but merely a *distance* marker. The marks produced by such a device, therefore, give an inaccurate and misleading time reference, unless the camera drive mechanism runs at one fixed invariable speed. Inasmuch as all spring motors, and all electric motors with the exception of the true synchronous alternating current motor, are subject to speed variations, it is impossible to assure that the paper or film shall always run at one fixed invariable speed. Although all precautions are being taken by manufacturers to assure a fixed speed, they all equip the machines with a time marking device. This is to serve as an index of speed variations, but from what we have already expressed, this device does not serve any purpose if it is not independent. If the speed of the camera did not vary and were absolutely fool-proof, which is impossible, there would be no necessity for a time marking device and additional mechanisms and expenditures. The paper could be marked when prepared or a ruler provided as a measuring device.

The solution of the problem of non-independent time markers may be synchronous alternating current motor to drive both the paper and the time marker. However, there are sufficient objections to the low-power synchronous motor to render its use, for camera drive purposes, unattractive.

Attempts have been made to insure constant speed of the camera drive, by incorporating some form of governor. The governor employed has almost always been of the friction brake type such as is used in phonographs. Such governors are not reliable, owing to the inevitable change in the character of the friction brake surfaces with continued use.

To illustrate and make clear the effects which we have discussed above,

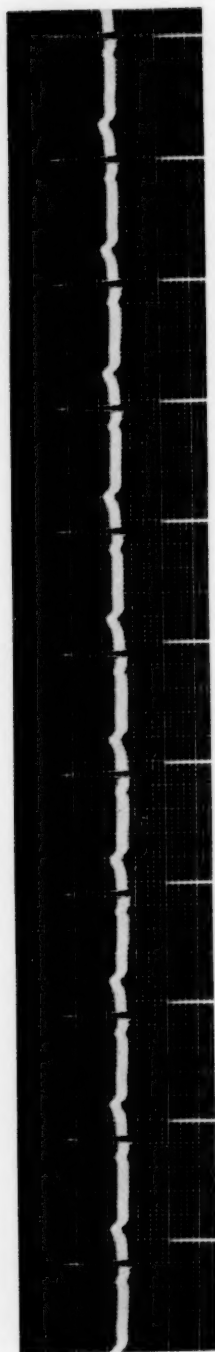


FIG. 3.

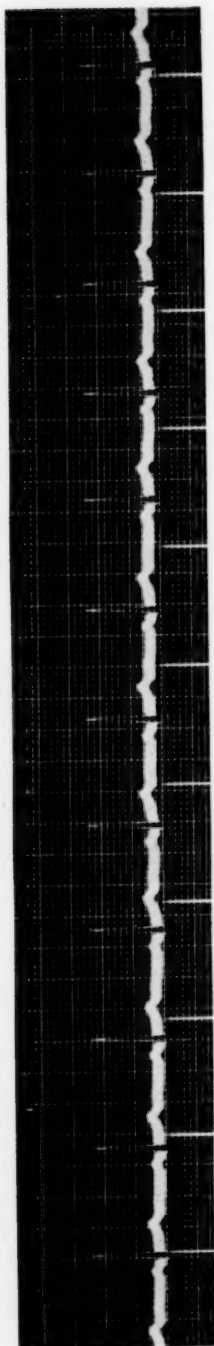


FIG. 3-A.

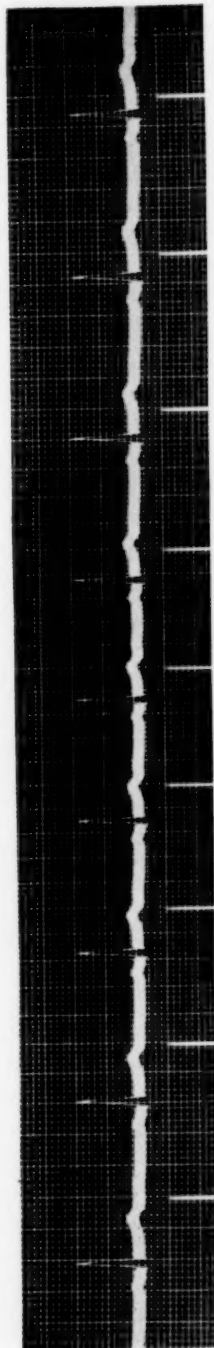


FIG. 4.

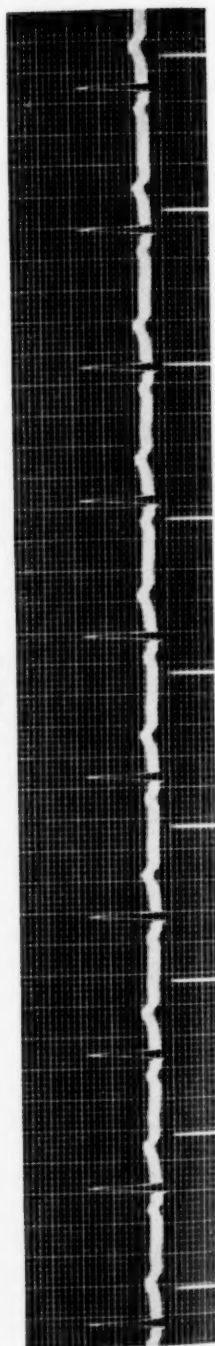


FIG. 4-A.

we show a series of tracings which illustrate clearly the errors into which the physician may be led in the interpretation of electrocardiographic tracings taken on equipments which incorporate these non-independent or interconnected time markers. These tracings were taken on two different equipments, one incorporating the recommended type of independent synchronous time marker, the other incorporating a non-independent time marker which was interconnected with and driven by the camera motor. The short marks along the lower edge of each tracing were made by an additional laboratory precision type time marker, marking accurate one second intervals.

*Figure 2.* Taken with independent time marker. Camera speed 25 mm. per second. Heart rate 61 per minute.

*Figure 2-A.* Taken with non-independent time marker. Camera speed 25 mm. per second (as nearly as it could be adjusted without a great deal of trouble). Heart rate approximately 68 per minute.

*Figure 3.* Taken with independent time marker. Camera speed 20 mm. per second, or 20 per cent slower than normal. Heart rate 59 per minute. It will be noted that although the camera was running 20 per cent slow the time marks on the tracing are still absolutely in step with the one second time intervals. In other words, the spacing between the time marks is 20 per cent less than at the normal speed of 25 mm. per second so that the timing is still absolutely correct.

*Figure 3-A.* Taken with non-independent time marker. Camera speed 20 mm. per second or 20 per cent slower than normal. In this case it will be noted that the "time" marks are spaced exactly the same distance apart as when this particular camera was running at its normal speed of 25 mm. per second (figure 2-A). Note, however, that the one second intervals which are imposed by an entirely independent time marker, are spaced considerably closer than in 2-A. The actual heart rate as measured from the correct one second time intervals is 66 per minute. However, if the heart rate is measured from the supposedly correct time marks on the tracing, the heart rate would appear to be about 86 per minute—an error of 30 per cent.

*Figure 4.* Taken with independent time marker. Speed of the camera was varied during the tracing from 19 mm. to 26 mm. per second—a change of 27 per cent. Please note that the spacing between the time lines varies in exact proportions to the speed of the camera. Note also that by measuring individual heart beats in relation to their adjacent time lines the heart rate is 59 per minute whether the time intervals are measured at the highest or at the lowest speed.

*Figure 4-A.* Taken with non-independent time marker. The camera speed was varied during the tracing from 16 mm. to 25 mm. per second—a change of 36 per cent. Note here again that the "time" lines are still spaced exactly the same distance apart as when this camera was running at 25 mm. per second (figure 2-A). Note, at the same time, that the one second intervals vary in their spacing with the camera speed. The equal spacing of the time lines in spite of the variation in speed of the camera gives

the effect of fairly pronounced arrhythmia. By measuring individual beats from their adjacent time lines the heart rate appears to vary from 65 to 103. However, if we measure the individual beats with relation to the adjacent independent one second time intervals, we find that the heart rate is approximately 66 per minute no matter where it is measured on the tracing.

#### SUMMARY

The foregoing demonstrates that in any photographic recording system such as that of an electrocardiograph, the only reliable and accurate time marker is one which is driven entirely independently from the camera driving system, by alternating current of controlled frequency or by intermittent direct current impulses provided by a tuning fork or similar device.

It also demonstrates that the so-called time markers which are connected to, and driven by, the same source of power which drives the camera are often unreliable and may be misleading since reliance can be placed in them only if they are checked and if necessary adjusted before and after each tracing is taken.

While interpreting an electrocardiogram it is important to investigate the type of instrument used. Should it reveal any abnormalities which may result from mechanical defects, the electrocardiogram should be checked with an instrument so scientifically and accurately constructed that mechanical irregularities can be recognized by means of a proper timing device.

The manufacturers of the less expensive instruments have made a fine contribution in making instruments available to a greater number of physicians. Improvement of the timing device will greatly enhance their value.

## THROMBOSIS OF THE ABDOMINAL AORTA; A REPORT OF FOUR CASES SHOWING THE VARIABILITY OF SYMPTOMS\*

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THROMBOSIS of the aorta, an uncommon and serious condition, has been recognized since Graham's description in 1814. Occasional cases were subsequently reported, so that Welch<sup>1</sup> was able to collect 59 cases of thrombosis and embolism in 1898. The number had increased to 94 in 1922<sup>2</sup> and Banovitch and Ira<sup>3</sup> in their summary of the literature cited 105 cases in 1928. Since then a number of cases have been reported yearly.

A majority of the reported cases were associated with chronic arterial and cardiac diseases. Many of them followed mitral stenosis and auricular fibrillation. The location of the thrombus varied, but the distal portion of the abdominal aorta was the most common site. Thrombi above the origin of the superior mesenteric artery were rare, while those near the bifurcation commonly extended into the iliac, femoral, popliteal or even the posterior tibial arteries—the so-called riding or straddling thrombi.

The usual symptoms described were those arising from a thrombus at or near the bifurcation of the iliac arteries. Severe to agonizing pain that arose in the loins and extended down both legs was the outstanding feature and indicated a rapidly forming thrombus. Intermittent claudication was said to be a common early sign in slowly forming obstruction; numbness, formication, pallor, coldness, areas of anesthesia on the legs or thighs, paraplegia and finally gangrene often followed. Either one or both lower extremities were involved. The type and extent of gangrene was dependent upon the speed and completeness of arterial closure and the inadequacy of collateral circulation. Diminution of pulsation of the larger arteries of the lower extremities was stressed as an important diagnostic sign.

The flexible symptomatology of the condition is well illustrated by the following cases. Case 1 was selected from private practise. Cases 2 and 3 were kindly supplied by Drs. H. O. Weishaar and Don C. Sutton, respectively, while Case 4 was taken from the records of the Research and Educational Hospital.

### REPORT OF CASES

#### THROMBOSIS SECONDARY TO A RHEUMATIC CARDITIS

*Case 1.* M. B., a white man, aged 45, complained of swollen joints and palpitation when first seen on February 5, 1935. As a boy of 10 he had a single attack of rheumatic fever that lasted for a month. It apparently left no traces but early in 1917 mitral stenosis was discovered. In 1923 he first experienced gradually increasing weakness and fatigue. He went to a clinic where he had his tonsils removed. Six

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weeks after the operation his hands and knees became acutely swollen and tender. This bout of polyarticular rheumatic fever lasted 10 months, involved most of the joints of the body and there was considerable residual deformity. It necessitated eight months further bed rest. In January 1925 he had several fainting attacks followed by signs of decompensation. An examination at that time disclosed a high grade mitral stenosis, aortic insufficiency, aortic stenosis, auricular fibrillation and rheumatic polyarthritis. After a short stay in the hospital and rapid digitalization he went home much improved. Slight benefit followed the administration of an especially prepared streptococcus vaccine. An autogenous vaccine was then used. The arthritis improved so that he was able to get out of bed and walk about. By July he spent much of his time out-of-doors walking about without discomfort.

That summer he called attention to a sharp cramp-like pain in his upper abdomen, associated with considerable belching and some nausea. He referred to it as "a burning in my solar plexus." A digitalis intoxication was not excluded despite the fact that none of the other toxic effects were present. Nevertheless, the drug was discontinued. During the next three days the pain slowly disappeared. It permitted him gradually to resume his former activities. Tonic doses of digitalis, 0.06-0.18 gm. (gr. 1-3) enabled him to carry on some of his business. On two occasions large doses of digitalis were given in an attempt to reproduce the abdominal pain. The pain could not be duplicated. A bradycardia of 60 to 64 beats per minute was the only effect.

On November 3, 1935, there was a second attack of acute abdominal pain. It was dull, heavy, cramp-like in character and definitely limited to the upper abdomen. There were no exertional, emotional or gastric antecedents. An irregular pulse rate of 115-120 beats per minute was noted. In addition to the previous cardiac findings there was an enlarged liver. The next morning the patient was considerably relieved by the belching of gas. By evening the pain was severe and colicky, associated with persistent nausea. The pain was then localized just above the umbilicus involving an area 5 cm. in diameter. Tenderness and rigidity soon appeared in this area. Large doses of dilaudid 0.003-0.009 gm. (gr.  $\frac{1}{20}$ - $\frac{3}{20}$ ) and morphine sulfate 0.016-0.032 gm. (gr.  $\frac{1}{4}$ - $\frac{1}{2}$ ) failed to relieve the pain. On the third day the rigidity extended down to the umbilicus. He vomited a small amount of bile-stained mucus. The blood pressure fell to 85 systolic and 60 diastolic. Both legs felt warm to touch and the cyanosis of the toes was no greater than that of the finger nails. Slight edema was present over the right tibia. At no time were there areas of paresthesia or anesthesia over the legs, thighs, or pelvis nor did the patient complain of any pain in these structures. He grew progressively worse, went into coma, and died on the fourth day of this illness.

Autopsy revealed an enlarged heart that weighed about 500 gm. The pericardial sac contained about 200 c.c. of clear fluid. Several easily ruptured adhesions were attached to the anterior surface of the right ventricle, conus arteriosus and pulmonary artery. The left atrium was greatly dilated. The auricular appendage was filled with firm red and red-brown thrombi which were attached to the wall between the trabeculae. Small irregular stripes and spots of yellow pigment were visible through the endocardium of the right side of the interventricular septum. The maximal thickness of left ventricular wall was 1.5 cm. The mitral valve barely admitted the tips of two fingers and measured 28 mm. Its superior surface was smooth, the leaflets showed definite fibrous thickening and along its margins were a few fine pink-yellow granules. The aortic valve showed great thickening of all three cusps, complete fusion and calcification of the anterior cusps and several fine granules along the line of closure adjacent to the commissures.

Extensive atheromatous degeneration of the thoracic aorta was present. At least 90 per cent of the intimal surface was covered by slightly elevated yellow plaques. Below the diaphragm many of these plaques were softened and ulcerated. Yellowish mushy substance was scraped from their surfaces. Firmly attached friable

thrombi forming thick polypoid masses covered the intimal surface of the aorta below the origin of the renal arteries. One of these extended for a few millimeters into the orifice of the right common iliac artery. Patches of fatty degeneration and small mural thrombi were seen in the first few centimeters of the left common iliac, but there was no appreciable obstruction of either iliac artery.

No noteworthy changes were found in the other organs of the body.

#### DISLOCATION OF A MURAL THROMBUS FROM AN ANEURYSM OF THE ABDOMINAL AORTA

*Case 2.* L. E. B., a male, aged 80 years, was admitted to the Evanston hospital on December 9, 1930, and died on December 17, 1930. He had retired from business 10 years previously. Four days before admission he had a dull pain in the epigastrium followed, the next day, by a sudden excruciating pain in the left upper quadrant. Large doses of morphine sulfate, 0.016 gm. (gr.  $\frac{1}{4}$ ) gave some relief from the pain. He was sent to the hospital where an examination revealed tenderness in the upper abdomen. A pulsatile mass the size of a grapefruit was found in the left hypochondriac region. Blood pressure was 132 systolic and 90 diastolic. Roentgenologic studies suggested an extrinsic cystic tumor pressing on the gastrointestinal tract. Five days after admission the pain in the left upper quadrant again was suddenly intensified. Nausea, vomiting and rigidity followed in succession. In an attempt to establish a diagnosis an exploratory laparotomy was performed. During the exposure of the mass, which later proved to be an aneurysm, a large mural thrombus was dislodged. The patient's condition immediately became critical and he died 18 hours later.

Autopsy showed moderate hypertrophy and dilatation of the heart. On cut section there were a few small gray fibrous areas, otherwise the myocardium appeared normal.

There was a high grade atherosclerosis of the aorta, especially the abdominal portion. Just above the aortic valves, the aorta measured 90 mm. in circumference. Its wall was inelastic and showed numerous raised yellow patches in the transverse and descending portions of the arch. These involved 60 per cent of the thoracic aorta and the thickenings were grouped about the orifices of the intercostal arteries. Some plaques were calcified. One shallow ulcer was present in the lower thoracic region.

The abdominal aorta was enlarged by a fusiform aneurysm that filled the left half of the abdomen. From a point opposite the renal arteries to the aortic bifurcation, the aneurysm had completely destroyed most of the posterior wall of the vessel. Within, the aneurysm was lined by a thick layer of lamellated blood clot. At the distal end of the enlargement near the bifurcation of the common iliac arteries there was a soft, granular thrombus that partially occluded the abdominal aorta. The muscular and fatty tissue surrounding the aneurysm contained large amounts of dark clotted blood. A large hematoma completely encased the left kidney.

#### THROMBOSIS FROM AN IMPAIRED CIRCULATION IN AN ATHEROSCLEROTIC ARTERY

*Case 3.* M. E. B., a woman, aged 71 years, entered the Evanston hospital badly decompensated. There was a history of arthritis during the past seven years which caused difficulty in locomotion. She had had hypertension for many years. Three years prior to entrance there had been the first break in cardiac compensation. After a month's stay in the hospital she had improved so that she was discharged. Another lapse in compensation necessitated her return to the hospital on October 11, 1930. The only other change in her condition from that at the first admission was a fall in systolic blood pressure from 238 to 186; the diastolic pressure remained 126 mm.

A week after entrance she had considerable abdominal pain and severe nocturnal dyspnea. For the next few days there was a diarrhea of four to six semi-formed

movements. No blood was found in the stools. With rest and medication she improved.

Her left leg suddenly became swollen a month after admission. The next morning the foot and leg were numb. Within a few hours they were swollen and red, then became cold, cyanotic and pulseless. There was a fever of 99.8° F., a leukocytosis of 22,000. The patient complained of severe pain in the left leg and later in the whole left side. There was a complete loss of tactile perception over the leg and extending along the inner side of the thigh. Blotchy areas of cyanosis developed the next day spreading over the heels, lateral aspect of ankle, and posterior surface of the left foot; gangrene followed that evening, advancing to the knee. The patient lapsed into coma and was spared the agonizing pain in the extremities. Similar bluish-pink to plum colored discolorations developed over the right ankle later that evening. They advanced involving the knee, thigh and buttock in succession. Early the next morning the patient died.

Autopsy revealed a moderate enlargement and dilatation of the heart. There were parietal thrombi of the right atrium and left auricular appendage. Both lower pulmonary lobes showed recent infarcts. Atherosclerosis and calcification of the aorta were most marked in the abdominal portion. Beginning at a point just below the inferior mesenteric arteries the abdominal aorta was completely closed by a thrombus which was adherent to practically the entire circumference of the wall, and extended downward into both common iliac arteries going into the internal and external branches on either side. The thrombus was softened in the portion lying between the bifurcation and a point two inches above it. The orifice of the right renal artery was partially closed by the thrombus.

#### RETROGRADE THROMBOSIS

*Case 4.* H. E., a 56 year old white male, complained of "shooting pains" in his legs and feet for five years before admission to the Research and Educational Hospital. The pain was worse when he stood for a long time or when he walked but it was relieved after a short period of rest. During the last three years these attacks of pain had increased in frequency and intensity. He noticed a small nodule on the dorsum of his left great toe in 1932. It became the seat of chronic inflammation which necessitated the amputation of the toe in December 1933. Soon afterward the lateral aspect of the left foot was infected and discharged pus intermittently for three years. A month before entrance he began to expectorate small quantities of muco-purulent sputum and experienced severe pain in his right chest. Dyspnea followed and together with the pains in his feet denied him any rest at night. On admission to the hospital he was very dyspneic, and had early gangrene of both toes with moderate edema of the ankles. Systolic blood pressure was 125, diastolic 98. There was limited excursion of the right lung, dullness and absent breath sounds. The apex beat of the heart was in the anterior axillary line and a systolic thrill and presystolic gallop rhythm were found. Both feet were reddish blue, purple and cold. Several draining sinuses clustered about the amputated stump of the left great toe. Neither the dorsalis pedis nor posterior tibial arteries could be felt, but there were weak pulsations over the popliteal artery. A roentgen examination of the left leg failed to show the arteries, but it did reveal a sclerosing periostitis of the fibula. The pain in his leg was so severe that it necessitated the almost constant use of morphine. Conservative management was tried for three weeks without avail, so a mid-thigh amputation of the left leg was performed. During this time there had been an increase in his dyspnea, and the percussion note over his right chest became flat. Clinical findings and roentgen films suggested a diagnosis of carcinoma of the right lung. Two weeks after the first amputation the right leg was removed at the upper third of the thigh. At this operation a tourniquet was not needed for the sclerotic vessels bled very little. He died 36 hours after the second amputation.

Postmortem examination disclosed a distended abdominal aorta. It contained a large thrombus at the bifurcation of the aorta, adhering to the intima of the vessel and extending into both iliac vessels. The thrombus varied considerably in consistency, the central portion being soft and the outer portions quite firm. The aorta was more adherent to the inferior vena cava than normal. A large thrombus was also found in the inferior vena cava which extended to the iliac veins, the right gluteal vein and the left femoral vein. A bronchogenic carcinoma of the right primary bronchus with metastases to the liver was also found.

#### COMMENT

The clotting of blood within its own vessels during life is an alarming condition. Its causes and mechanisms have been adequately described by many. Changes in an organ or part secondary to deprivation of blood flow by a thrombus are perhaps of greater interest. Sudden cessation of blood flow in one of the larger vessels produces a symptomatology that is dependent upon the anatomy of the part, the extent of collateral circulation and the rapidity of thrombus formation.

In the past the entire symptomatology of thrombosis of the abdominal aorta has been ascribed to the stoppage of blood flow through the iliac and femoral arteries. The sharp shooting leg pains, the abolition of femoral, popliteal or posterior tibial pulsations, and the ascending gangrene of the legs were cited as supporting evidence. Welch<sup>1</sup> believed the absence of pulsation in the arteries of the lower extremity was the sign of greatest value. This sign is not, however, diagnostic as it occurs in severe anemias, arteriosclerosis and calcification of the larger arteries of the lower extremity, coarctation of the aorta, and extensive thrombophlebitis.

Coincident with the arrest of flow to the legs there are frequently ischemic changes in the spinal cord. These have not received sufficient attention. Most of the older textbooks and literature described in detail the vascular changes in the larger arteries, but scarcely mention a similar pathologic invasion of the smaller arteries, e.g., the intercostal or lumbar arteries. Ligation of the abdominal aorta below the renal arteries (Stenson's experiment) resulted in a paraplegia which was shown to follow an ischemia of the cord. These experiments have been frequently confirmed using a variety of animals. Recently, the problem has been critically re-investigated by Reichert, Rystand, and Bruck.<sup>4</sup> Ligation of one or more paired lumbar arteries in dogs, they found gave results almost identical with Stenson's experiment. Further, four patients were reported by these authors with Déjérine's syndrome, viz., intermittent claudication of the thighs, weakness of both lower extremities, and absence of neurologic signs and of syphilis, whose roentgen-rays revealed arteriosclerosis of the lower abdominal aorta. It was their opinion that the claudication resulted from ischemia of the cord due to occlusion of the spinal branches of the lumbar arteries. In fact, an ipsilateral occlusion of one or more lumbar arteries was observed in a patient who had a unilateral claudication.

A brief review of the anatomy of the lower abdominal aorta would be pertinent. Branches of the abdominal aorta are said to be segmentally arranged. It is believed that three sets of vessels arise from each segment: an anterior, lateral and posterior. The anterior set are reduced by fusion or degeneration to single vessels as the celiac, superior mesenteric and inferior mesenteric. Most of the lateral set disappear except the renal, suprarenal, and spermatic, while the posterior or third set become the paired lumbar arteries, which serve as homologues of their neighbors above, the intercostals.

The lumbar arteries arise from the posterior aspect of the aorta, wind transversely around the bodies of the vertebrae, behind the sympathetic trunk to the spaces between the transverse processes, where a large branch (*ramus dorsalis*) is given off, while the remainder of the vessel courses forward to terminate by anastomosis with other anterior abdominal arteries.<sup>5</sup> There are four branches of the lumbar arteries. A vertebral branch (*ramus vertebralis*) which sends twigs to the psoas, quadratus lumborum and oblique muscle of the abdomen. The dorsal branch (*ramus dorsalis*) which passes backward between the transverse processes to divide into three branches: a lateral that supplies the multifides; a medial that supplies the sacrospinalis muscle and a spinal which supplies the tissues of the spinal canal and the spinal cord. A fourth branch of the lumbar arteries is the renal (*ramus renalis*) which goes to the capsule of the kidney.<sup>6</sup>

It is thus evident that cessation of blood flow through the spinal branches (*rami spinalis*) of the lumbar arteries will produce the focal lesions of the spinal cord described above.<sup>7</sup> Recognition of the condition is difficult. Even though there has been much written concerning thrombosis of the larger branches of the abdominal aorta, the condition is difficult to diagnose. Trotter<sup>8</sup> in an excellent monograph on the subject remarked that superior mesenteric thrombosis was recognized before death or post mortem only 13 times in 360 patients. Inferior mesenteric thrombosis is an equally perplexing diagnosis, while the differentiation between them, "need not detain us long as it is a refinement that is not likely to be attempted in a disease that is itself difficult to recognize." Some notice has been given to thrombosis of the renal arteries but similar changes in the supra-renal, spermatic or ovarian, or lumbar arteries have scarcely been mentioned.

Thrombosis of the abdominal aorta is a relatively infrequent, though by no means a rare clinical entity. Its approximate incidence may be judged by the records of the Research and Educational Hospital, where it occurred once in 1047 post mortems. While it is true that patients are selected for admission according to their teaching value, yet in none has thrombosis of the aorta or its branches been suspected. Consequently the above ratio may be taken as a fair indication of the incidental frequency of the condition in a general hospital.

Recognition of the condition is dependent upon the rapidity and extent of arterial closure of the aorta, when the usual symptoms make its identifi-

cation easy (Case 3). Less rapidly forming obstructions give a delayed symptomatology as in Case 4. A much slower process as the gradual erosion of an abdominal aneurysm may be symptomless for some time. Sudden detachment of a large mural thrombus in an aneurysmal sac may occlude the distal orifice sufficiently to give a picture of acute obstruction (Case 2). Slowly degenerative atherosclerotic changes are most difficult to recognize, and since the process is generalized thrombi are likely to occur in a variety of places throughout the vascular tree at irregular intervals. Such vascular occlusions in more peripheral vessels may confuse the picture and cause the overlooking of a thrombosis of the abdominal aorta.

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## STUDIES IN DYSTROPHIA MYOTONICA. IV. MYOTONIA: ITS NATURE AND OCCURRENCE \*

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AFTER grasping an object with great force, a normal person is occasionally conscious of a little difficulty in relaxation. Because this difficulty is slight and occurs only under unusual circumstances, it is in no way disabling and therefore scarcely noticeable. As a result of an inherited defect, other persons are unable to relax their muscles rapidly after contractions of ordinary strength. Under these conditions the muscles remain contracted for some time after the effort to contract them has ceased. Because the contraction persists during what is normally the phase of relaxation, the difficulty appears as a slowness in relaxation. This prolonged contraction or delayed relaxation is called myotonia. The duration of the contraction varies with the strength of contraction and the degree of involvement of the muscle; the stronger the contraction the more marked the myotonia. In some persons, however, a very strong contraction will result in only slight myotonia; in others, even very weak contractions are associated with marked myotonia. A minute or more may, at times, be required for the muscle to return to its resting state.

Depending on the location of the involved muscle, affected individuals show varied disabilities. Involvement of the muscles of the forearm and hand results in a difficulty in releasing objects once grasped. The carpenter may not be able to release his hammer or the brakeman the handle of the box car. Involvement of the muscles of mastication may result in the jaw remaining shut for several seconds after biting down on some firm food. Involvement of the muscles of the legs makes walking difficult. Involvement of the eye muscles may result in the eyes remaining fixed after a sudden glance to the side. When most of the muscles of the extremities are involved, a sudden movement such as results from fright, may produce a marked myotonia in both flexors and extensors and the affected individual, unable to move his limbs, falls to the ground "as a log." Although associated with a feeling of stiffness, myotonia is not painful.

Fortunately, myotonic muscles show the saving characteristic that each time the muscle is contracted the myotonia becomes less and after several contractions temporarily disappears (figure 1). Thus, although on the first bite the muscles of mastication may require many seconds for relaxation, the second bite will require less time, the third still less, and so on, until the in-

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dividual can chew his food with no evident difficulty. On starting to walk, the first few steps are difficult but the difficulty becomes less with each step until it is entirely gone. The sudden bringing into use, however, of a new



FIG. 1. Movements of the thumb in a patient with dystrophia myotonica; recorded by means of an ergograph and kymograph. Only the muscles producing the upstroke on contraction showed myotonia. The myotonia is evident as the prolongation of relaxation or downstroke. B was taken 10 minutes after A.

Note: the decrease in myotonia in successive contractions and the return of the myotonia after 10 minutes' rest. Time in seconds.

set of muscles results in renewed difficulty, as, for example, beginning to run after having walked. As a corollary of this improvement with repetition of contraction, it follows that the myotonia returns if the muscle is permitted to rest and that myotonia is greatest on the first contraction after a period of rest.

If a muscle which shows myotonia is stimulated to contract by striking it with a percussion hammer, the contraction shows certain peculiarities, most conspicuously a prolongation of the phase of relaxation. The dimple or

furrow formed by the contraction of the stimulated fibers remains visible for many seconds. If small muscles are struck, such as those of the thenar eminence, the muscles often contract as a whole. In such instances, a slow phase of contraction in addition to a slow phase of relaxation is evident. The myotonia decreases with repetition of the percussion but does not usually disappear.

The same phenomenon is seen on producing muscular contraction with an electrical current. Faradic currents of sufficient strength produce myotonic contractions after both nerve and muscle stimulation. With the galvanic current the myotonic contraction is usually evident only after muscle stimulation.

The myotonia seen following voluntary contractions has been called "active or voluntary myotonia," that following mechanical stimulation, "mechanical myotonia," and that following electrical stimulation, "electrical myotonia." The total response of the muscle to electrical and mechanical stimulation has been termed the "myotonic reaction." Any person who shows voluntary myotonia in a few muscles is apt to have mechanical and electrical myotonia of wider distribution.

It is important to note that in each of the above instances the contraction has been voluntarily produced. Myotonia is most commonly confused with persistent contractions of involuntary nature, such as are produced by tetany or irritative nervous system lesions. Involuntary contractions are probably no more common in patients with myotonia than in other persons and when they occur, represent an accidental association.

Voluntary myotonia is affected by certain drugs and a number of conditions, psychic and environmental. Possibly because of an increased strength of contraction, myotonia is much more evident during excitement or fright. It is usually worse under the influence of cold and is improved by warmth. It is not closely dependent upon circulatory conditions.<sup>1</sup> Quinine is a specific for the relief of myotonia, and when given by mouth or intravenously in sufficient dosage, almost completely but only temporarily abolishes myotonia.<sup>2, 3</sup> The same is true of quinidine.<sup>1</sup> Epinephrine given subcutaneously or intravenously temporarily decreases myotonia in patients with dystrophia myotonica<sup>1</sup> (figure 2). Its effect in patients with myotonia congenita requires further investigation. Calcium given intravenously produces a less marked but definite decrease in myotonia.<sup>1</sup> Probably as a result of the mobilization of epinephrine, insulin decreases myotonia when symptoms of hypoglycemia are present.<sup>1</sup> Prostigmin increases myotonia.<sup>3, 4</sup> Potassium chloride by mouth is said to increase myotonia.<sup>3, 4</sup>

In our studies of dystrophia myotonica, much time has been devoted to investigation of the nature of the defect in myotonia. Myotonia is most commonly compared to veratrine contracture. If a strip of frog's muscle is immersed in a veratrine solution, stimulation no longer produces a rapid contraction and relaxation but results in a rapid contraction followed by a slow relaxation very similar to that seen in myotonia. The relaxation be-

comes more rapid if the stimulation is repeated, but returns to its original level after a period of rest. The resemblance to myotonia is again striking. A similar response to strong electrical stimulation of certain highly susceptible muscles of the frog in the absence of veratrine is known as Tiegel's contracture. The same phenomenon, moreover, can be produced in susceptible frog muscles by suitably spaced electrical stimuli delivered to the nerve supplying the muscle. This is the neuromuscular contracture of Bremer.<sup>5</sup>

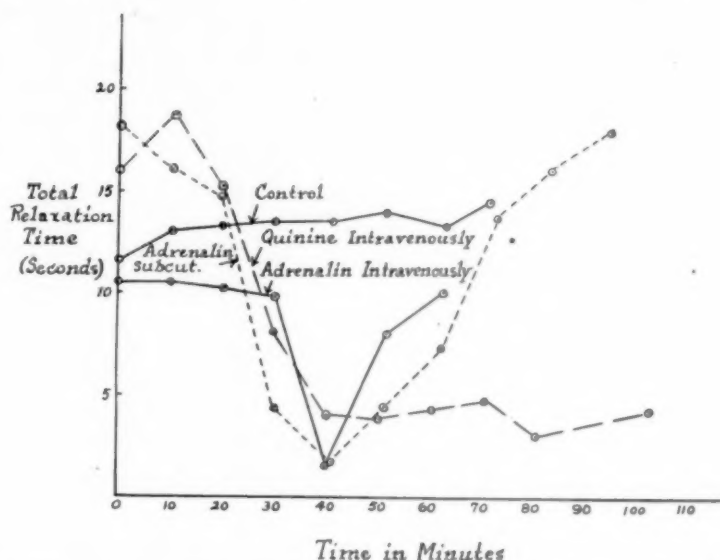


FIG. 2. Effect of adrenalin and quinine on myotonia. Tests of myotonia made at about 10-minute intervals. "Total Relaxation Time" obtained by totalling the times required for relaxation of the first three contractions in each test. Control—at arrow 0.1 c.c. of distilled water was injected. Quinine—at arrow 10 grains of quinine dihydrochloride were injected intravenously. Adrenalin subcutaneously—at arrow 14 mm. of adrenalin hydrochloride (1:1000) were injected. Adrenalin intravenously—at arrow 1½ mm. of adrenalin hydrochloride (1:1000) were injected.

Note: the marked but very fleeting decrease in total relaxation time produced by adrenalin injected intravenously; the marked and somewhat more prolonged effect produced by adrenalin injected subcutaneously; and the marked and prolonged effect of the quinine.

The term "contracture" distinguishes the foregoing type of contraction from a tetanus. A muscle stimulated at such frequent intervals that it remains in a persistent state of contraction is said to be in tetanus. The stimuli cause the fiber as a whole to contract and produce waves of electrical change which travel throughout the length of the muscle fiber. In a contracture the contraction persists for an abnormally long time after the stimulus producing the contraction has ceased acting. The wave-like electrical variations are not present and the shortening is not propagated through the fiber as in the tetanus but may remain localized.<sup>6</sup> Contracture and tetanus are believed by most investigators to involve the same contractile mechanism and the same energy metabolism. Normal muscles are thus seen to possess the property to respond under certain conditions by a contracture. This prop-

erty of responding by contracture varies in degree in different muscles and can be brought out by some drugs.

The relationship of myotonia and contractures is emphasized by the work of Mosso<sup>7</sup> and of Schäffer<sup>8</sup> on the electrical stimulation of the muscles of man. They found that on repeated stimulation of the forearm muscles with strong electrical currents, they could produce a Tiegel's contracture in many normal individuals. It is, therefore, evident that in the human muscle, under certain conditions of stimulation, the capacity to respond by contracture is present. All of the types of contractures mentioned as well as myotonia show the property of fatigability, that is, decrease in duration with repetition of the contraction. The similarity in response to drugs of myotonia and of the contractures is shown in table 1. It may reasonably be concluded that myotonia is closely related to the group of contractures and that the defect in myotonia may be an inherited increase in the tendency of the muscle to respond by contracture.

TABLE I  
Comparison of the Effect of Drugs on Myotonia and Several Contractures

	Decrease with Repetition	Quinine	Adrenalin	Atropine	Eserine Prostigmin	Calcium
Myotonia	Present	Decrease	Decrease	Decrease?	Increase	Decrease
Tiegel's Contracture in Man	Present		Decrease	Decrease	Increase	
Tiegel's Contracture in Frogs	Present		No Effect	Decrease		
Veratrine Contracture	Present	Decrease	No Effect	Decrease		Decrease
Neuromuscular Con- tracture	Present	Decrease	No Effect	Decrease	Increase	

#### OCCURRENCE OF MYOTONIA

*Myotonia Congenita.* Myotonia is the well known and striking symptom of Thomsen's disease or myotonia congenita. This hereditary condition is transmitted as a single factor dominant; that is, one half of the children of a person affected with myotonia congenita are likewise affected but none of the children of unaffected members of the family manifest the disease. The myotonia usually begins in the first decade, occasionally in the second, and persists throughout life although in some families it has been reported to become less severe as the individuals become older. Most of the skeletal muscles are involved and the affected muscles show a hypertrophy which gives these persons a marked athletic appearance out of proportion to their actual strength. On initiating any new movement they are brought up short by the myotonic contractions and soon learn to avoid sudden move-

ments. By "warming up" before attempting any marked exertion, many embarrassing situations are avoided. Myotonia congenita is not a fatal malady but until the discovery of the beneficial effect of quinine, little could be done to ameliorate the disability. Quinine in doses of 15 to 30 grains per day by mouth affords great relief.

*Dystrophia Myotonica.* Although less generally known to the medical profession than myotonia congenita, this condition is much more common. Many of these cases are diagnosed myotonia congenita and many more, progressive muscular atrophy. The disease appears to occur rather explosively in many members of one generation, the members of the previous generation being apparently normal. Examination of family trees shows, however, that the parents of dystrophic patients do show evidences of the disease and it is our belief that the disease is transmitted as a dominant characteristic modified, however, by "progressive inheritance." Parents of patients with the disease have a mild form of the disease but affected children of patients have the disease in a more severe form and at an earlier age.<sup>9</sup>

In this disease the myotonia is limited in distribution and constitutes a relatively unimportant part of the symptom complex. It occurs mainly in the hand grasps, occasionally in the muscles of mastication and in the legs. Rarely it may be widespread. The most important feature of the disease is the progressive muscular atrophy. In early stages this atrophy shows a characteristic pattern of involvement which includes the muscles of the face, the sternocleidomastoids, the muscles of the forearm, the quadriceps, and the dorsiflexors of the feet. In more advanced stages most of the muscles of the body are involved. In addition to the myotonia and atrophy, many other dystrophic changes occur. A rather characteristic cataract is almost always found if slit lamp examination is done. Testicular atrophy, baldness, and low basal metabolic rate frequently form the remainder of the picture. The condition progresses slowly but inexorably and, unlike myotonia congenita, many of these patients die of the disease. Quinine improves the myotonia; cataract operation improves vision; but nothing has yet been found to stay the progress of the disabling atrophy.<sup>10</sup>

*Myotonia Congenita Intermittens* and *Paramyotonia Congenita* (Sölder-Schott). Rare families have been described whose affected members are normal in warm weather but show muscular difficulties under the influence of cold. In some families myotonia alone occurs, in others the myotonia is associated with a marked muscle weakness, and in still others the muscle weakness occurs alone. The condition is inherited and appears to be a single factor dominant. The muscles involved are mainly those of the upper extremities and of the face; the legs are involved only in severe cold. When the cold results in myotonia without weakness, it is preferable to label the condition *myotonia congenita intermittens*.<sup>11</sup> When a marked muscular weakness occurs in addition to the myotonia the condition has usually been called *paramyotonia congenita* because of confusion with the disease de-

scribed by Eulenburg.<sup>12</sup> In paramyotonia congenita as described by Eulenburg there are no myotonic contractions in warmth or cold and the essential feature is the occurrence in the cold of spontaneous cramps followed by a weakness simulating paralysis. One such family has been described in America by Rich.<sup>13</sup> Rather than use a new name for the disease in which myotonia occurs in addition to weakness, we have retained the name of paramyotonia congenita but qualified it by adding the names of two men who have described such families. We may thus speak of the paramyotonia congenita of Sölder<sup>14</sup> and Schott<sup>15</sup> and the paramyotonia congenita of Eulenburg.

*Myotonia Acquisita.* Many cases have been reported in the literature in which myotonia has occurred sporadically following an injury or illness in individuals having no hereditary background. In 1934 Krabbe<sup>16</sup> collected 34 such cases from the literature and added one of his own. Examination of such cases shows that they fall into three groups:

(1) Patients in whom the condition described is definitely not myotonia, but various types of intention spasms and involuntary contractions which do not fulfill the criteria for myotonia.

(2) Patients in whom the hereditary features have been overlooked because of incomplete investigation. The nature of the inheritance in dystrophia myotonica is such that it is not always evident. Any patient showing any evidence of the atrophy characteristic of dystrophia myotonica or the cataract must be excluded from the group of acquired myotonias. When it is recalled that the myotonia may be the earliest sign of dystrophia myotonica it is evident how cautious one must be in making a diagnosis of myotonia acquisita. In families with myotonia congenita the patient's statement that none of the other members of the family are affected is not sufficient to rule out heredity. The members of families affected with myotonia show the same variation in the degree of involvement which is characteristic of members of families affected with other hereditary conditions. It is well known, for example, that in some members of polydactylous families the defect can be recognized only by roentgen-ray. Likewise, myotonia may be so mild in the affected parent as to be overlooked.

(3) A very small group of patients in whom it seems possible that a true myotonia has temporarily manifested itself after some injury and in whom the hereditary factor appears ruled out.

It seems safe to conclude that, if myotonia acquisita does occur, it is quite rare, unless one considers the syndrome described below as falling under that heading.

*Syndrome of Hypothyroidism, Muscle Hypertrophy, and Myotonia.* Examination of the literature shows approximately a dozen cases<sup>17-25</sup> in which hypothyroidism, muscle hypertrophy, and myotonia have been combined to form a remarkably uniform picture. They have been reported as

cases of myxedema with unusual muscle phenomena, as cases of myotonia congenita, and as cases of muscle hypertrophy of unknown origin.

The hypothyroidism is usually very evident, with the characteristic facies, the skin changes, the mental changes, and even the cardiovascular changes. The hypothyroidism may be congenital, follow thyroidectomy, or occur spontaneously in adults of either sex and of any age.

The muscle hypertrophy is most striking in infants but occurs also in adults. Although usually quite generalized it is often more marked in the extremities. The muscles are firm and the muscle strength does not correspond to the bulk.

Not all forms of myotonia are always found. The mechanical myotonia is most marked and most frequently reported. Voluntary myotonia is not marked in any case and often reported as absent. Electrical myotonia is usually present but differs in minor details from the electrical myotonia seen in myotonia congenita.

In many patients evidences of hypertonicity of the muscles are present. In the infant severe spasms sometimes occur and resistance to passive motion is present. In adults hypertonicity is evident as painful contractions which come on usually with sudden or forcible movements.

With thyroid therapy marked improvement occurs in the muscle symptoms as well as in the symptoms of hypothyroidism. From the effect of thyroid therapy it must be concluded that the entire syndrome is the result of thyroid deficiency. We have been investigating patients with myxedema and have found repeatedly a clear-cut although short mechanical myotonia. It is our belief that probably all patients with marked myxedema show slight or moderate evidence of the above changes but that the entire syndrome occurs only in persons with some inherited defect. This defect may not be the same as that which results in true myotonia.

#### SUMMARY

1. The muscles of some persons remain contracted for an abnormally long time after voluntary effort to contract them has ceased. This muscular abnormality is called myotonia and is manifest as a delay in muscular relaxation.

2. In a series of contractions myotonia diminishes each time the contraction is repeated. Correspondingly it is worse after a period of rest. Myotonia is not painful; it increases with increase in force of contraction.

3. Myotonia associated with voluntary contractions is called "active or voluntary myotonia." Myotonia associated with contractions produced by mechanical or electrical stimuli is known respectively as "mechanical myotonia" and "electrical myotonia."

4. Voluntary myotonia is decreased by quinine, by adrenalin, by calcium given intravenously, and by insulin when symptoms of hypoglycemia are present.

5. A comparison of the characteristics of myotonia with those of several contractures suggests that myotonia may be a contracture.
6. Myotonia occurs classically in myotonia congenita.
7. Myotonia occurs most commonly in dystrophia myotonica.
8. Rarely myotonia occurs only under the influence of cold.
9. Myotonia occurs infrequently in persons without a hereditary background.
10. In the severely hypothyroid state some persons show, in addition to the usual signs of hypothyroidism, muscular hypertrophy and myotonia.

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## CARDIOVASCULAR EFFECTS OF LARGE DOSES OF METRAZOL AS EMPLOYED IN THE TREATMENT OF SCHIZOPHRENIA \*

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SINCE von Meduna<sup>1</sup> first reported his success in the treatment of schizophrenia by the induction of convulsions with metrazol, his method has enjoyed considerable popularity, and has been employed in many hundreds of cases.

His method consists essentially in the repeated (three times weekly) induction of severe epileptiform convulsions of a specific type by the rapid intravenous injection of large doses of metrazol (pentamethylenetetrazol, formerly known as cardiazol), in a 10 per cent aqueous solution. The initial dose usually employed is 3 to 5 c.c. and it is usually increased progressively so that convulsions are regularly obtained—until a course of treatment producing 20 to 30 convulsions has been administered. Such a schedule at times necessitates pushing up the individual injection dose to amounts as high as 25 c.c., and it is quite usual for doses of 12 to 15 c.c. to be reached in the average case.

In view of the original introduction and use of this drug as a cardio-respiratory stimulant (as the name cardiazol implied), and then generally only in doses of 1 to 2 c.c. administered subcutaneously or intramuscularly, it is not surprising that we frequently hear expressed concern about the possible danger to the heart of employing such massive doses intravenously. The purpose of this paper is to supply a definite answer to this question.

A priori one might assume that there are no significant dangers to the cardiovascular system inherent in the metrazol treatment because in the numerous cases treated no serious cardiovascular complications have been reported.

The solitary instance of cardiac death reported in the literature (L. von Angyal and K. Gyárfás<sup>2</sup> obviously should not be attributed to the therapy but to improper case selection: A female patient, aged 31, was given her second injection, 0.7 gm. of metrazol and did not have a seizure; however, one-half hour later she suddenly collapsed and died. Autopsy showed an *old* aortic insufficiency and myocardial degeneration.

A survey of the published literature affords the following sketchy information: Friedman<sup>3</sup> states: "The entire sympathetic nervous system is

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stimulated: for example, rapid changes of skin color, goose flesh, profuse sweating, changes in cardiac rate and blood pressure, stimulation of the entire alimentary tract, bladder incontinence, ejaculation." He does not specify what the cardiovascular changes are.

Finkelman et al.<sup>4</sup> state: "The blood pressure rises from 20 to 60 mm. of mercury during the seizure and drops to its normal level in from 10 to 30 minutes."

L. Kruger<sup>5</sup> remarks: "Pulse rate and quality were but slightly affected. Cardiac function showed no more changes than occur with any convulsion."

L. v. Meduna<sup>6</sup> cites Lax as follows: "An electrocardiogram was taken in 11 patients who underwent cardiazol therapy. Sometimes the electrocardiogram was taken before, and sometimes after the convulsion. In 5 cases an electrocardiogram was taken during the convulsion and then 10-15 minutes afterwards. We could find no noteworthy changes from the ones taken before the convulsions and serving as controls. As a further check, 8 patients had electrocardiograms taken 2-4-6 or 1-3-5 hours after the convulsion. In 4 cases there was a minimal depression of the T-wave as compared with the records made before the convulsion. There was no change detected in the P-wave or ventricular complex in height, or time interval, nor any alteration in the rhythm or signs of ectopic origin. In conclusion we may say: Up to the present our investigations seem to show no changes in the electrocardiogram indicative of myocardial damage after cardiazol convulsions."

In a paper devoted primarily to the effects of crystalline insulin on the blood pressure and electrocardiogram, Heinrich and Sussner<sup>13</sup> state that when metrazol was administered the decrease in blood pressure, which lasted only seconds, was followed by an increase that persisted for minutes. Electrocardiographic tests frequently revealed that the T-wave, which had become lower under the influence of crystalline insulin, showed a tendency to rise again. The effect of metrazol on the frequency varied in that acceleration or retardation occurred.

Hadorn<sup>14</sup> also has made some electrocardiographic studies in metrazol shock. He found that metrazol shock therapy does not cause the same electrocardiographic changes as does the insulin shock; nevertheless it does cause changes, particularly in the auricular activity. The electrocardiograms that are made after metrazol shock reveal chiefly sinus tachycardias and a tendency to extrasystoles and auricular fibrillation. Changes in the S-T section and in the T-wave, which characterize insulin shock, are absent.

A review of the literature on work performed with metrazol on experimental animals also discloses quite meager and, in some respects, conflicting data as regard its cardiovascular effects: Thus, E. A. Müller<sup>7</sup> reports: "Experiments on intact animals (dogs) showed that with strong depression of the heart and circulatory activity by deep narcosis, cardiazol produced a definite long lasting elevation of blood pressure and minute volume to the normal level. The increased blood pressure is not merely the result of the

increased minute volume but is also due to increased peripheral resistance. The heart adapts immediately or in a short time to the increased circulatory work-load. The cause of this adjustment is *not* a direct effect of the cardiazol on the heart, as is shown by heart-lung preparation experiments, but rather of an improved coronary circulation, which is partly a result of the increased blood pressure, and partly a consequence of the direct widening effect of cardiazol on the coronary vessels." This worker conducted his experiments on only three dogs, and claims he secured an increased coronary flow "ranging from 1 per cent to 22 per cent," using doses of metrazol ranging from 10 to 100 mg. intravenously. Thus, his maximum dose corresponds to a dose of 9 c.c. (0.9 gram) applied to a 60 kilogram human. He made no electrocardiographic studies.

On the other hand, Stoland and Ginsberg<sup>8</sup> state: "Data on the intact animal warrant the conclusion that metrazol has no important effect on coronary flow, blood pressure, or heart rate." They also had worked on dogs and their maximum dose corresponded to a dose of 6 c.c. (0.6 gram) for a 60 kilogram human.

As regards the use of metrazol in the routine combating of postanesthetic depression, K. Schlaepfer<sup>9</sup> states: "Metrazol does not appear to have a local effect on the blood vessels, but a central stimulation brings about an increase in the tone of the vascular wall, followed by a rise of a *lowered* blood pressure. Apparently, the drug has little or no effect on the normal blood pressure of a normal individual."

Since the sources quoted above present so few detailed physiological or electrocardiographic studies of the effect of the metrazol treatment on the cardiovascular system, we feel that more information should be made available.

Our case material consisted of 14 psychotic male patients ranging in age from 26 to 46 years. One patient's age fell in the third decade, two fell in the fourth, and the remainder in the fifth decade, so that their average age was well over 40. Ten of the patients had had one or more previous complete courses of Sakel's insulin treatment, but in every case at least two months had elapsed since the insulin treatment was completed before metrazol was begun. Only two cases (numbers 6 and 7) had had no previous pharmacological shock treatment. We shall group our observations under the two headings of clinical and electrocardiographic findings:

### I. CLINICAL FINDINGS

The dramatic picture of the patient's appearance during the metrazol convulsion has often been adequately described in the literature. Moreover, various workers in this field have made color movies of the seizures and thus graphically recorded the color changes. From all such studies it is clearly apparent that there occurs during the metrazol seizure a profound activation of various vasomotor centers, which is reflected by generalized or regional

blanching or suffusion of different areas of the body surface. It must be borne in mind, however, that the color changes observed are the result not only of the vasomotor activity, but also of the cyanosis which usually develops during the tonic phase of the seizure (and which may persist for some time thereafter because of mechanical obstructions in the air passages), and that they further are modified by the ischemic and congestive changes produced in the skin areas overlying the violently contracting muscles. The variable pictures seen in different patients, and the evident tendency for similar series of vasomotor changes to repeat themselves in the same patients, may be accepted as an indication that the precise nature of the vasomotor reaction in any individual is directly dependent on the particular pattern of vasomotor organization of that individual. It has been our experience that in those instances where the injection of the drug was followed either by no seizures at all or by only an abortive (*petit mal*) type of reaction, the vasomotor changes were less marked or even absent.

Palpation of the pulse usually shows a slight to moderate acceleration (10 to 30 beats per minute) immediately after the seizure, and quite frequently the appearance of some irregularity (occasional extrasystoles) which invariably subsides entirely in a minute or so. Only rarely does a more marked tachycardia (140 to 160 per minute) appear for a minute or so after the fit, but this, too, soon subsides (see items 9 and 10 in the electrocardiogram table). The volume of the pulse is usually well maintained, particularly after the irregularity has disappeared.

Auscultation is obviously impractical during the stormy convulsive episode, but after the breathing has quieted down sufficiently during the post-convulsive phase, the heart sounds are invariably found to be of good quality and regular in rhythm. Careful auscultation for murmurs is also impractical during the postconvulsive comatose, semicomatose, and confused states, so that we made most of our observations for murmurs in the afternoon three to four hours after the metrazol injection. At that time we quite frequently found evidence of the development of the aortic dilatation phenomenon analogous to that which we described in an earlier paper concerned with the cardiovascular effects of insulin treatment.<sup>10</sup> That is, in every treated patient who was properly coöperative we could detect murmurs varying from the faintest systolic blow to a quite marked to and fro blowing murmur at the aortic area and left border of the sternum. The murmurs were very faint and practically insignificant (listed as one plus) in half of our patients. When they were more definite (listed as two to three plus) in the other six patients, they were not as marked as the murmurs these same patients had shown while under the insulin treatment, and similarly these same patients did not show as great an increase in pulse pressure while under metrazol treatment as they had shown while under insulin treatment. Since the two patients who had not been previously treated with insulin fell in the group which showed only minimal (one plus) murmurs, we cannot conclude that metrazol *alone* is a profound sympathetic (adrenalin-mimetic) stimulant

of the cardiovascular apparatus. It may be that in those cases which were more sensitive it had merely reactivated a latent sympathetic susceptibility which had originally been markedly augmented by the previous course of insulin treatment.

In order to determine the effects of metrazol injections on the blood pressure, studies were made in connection with some (72) metrazol injections administered to 12 different patients. Thirty-three of these observations were made on patients who were receiving metrazol alone, the remainder being made on patients who received metrazol in conjunction with insulin during the third hypoglycemic hour. All blood pressure readings were made by the same observer (N. M.) by the auscultatory method, using a mercury sphygmomanometer. Readings were made in each instance immediately before the metrazol injection, and then again as soon as possible after the convulsive reaction had ended. This second reading was usually feasible within 5 to 10 seconds after the last convulsive twitch. In many cases subsequent readings were taken at minute intervals. In those instances where a typical "grand mal" or "petit mal" type of convulsion did not result from the metrazol injection, the second reading was taken within one minute after completion of the injection. The position of the sphygmomanometer cuff was not changed between the two readings, the intravenous metrazol injection being given into the other arm.

We have listed the results of the blood pressure readings in tabular form according to the type of metrazol reaction which followed the injection. In table A we have listed the cases in which the injection was followed *only by slight stimulation*, as manifested by a slight twitching of the eyes, startled expression, and subjective "dazed" feeling. In table B we have listed the cases in which the injection was followed by a "*petit mal*" type of reaction as manifested by more or less prolonged definite clonic movements often associated with marked mental excitement and not followed by any appreciable state of coma. In table C we have listed the cases in which the injection was followed by the typical metrazol "grand mal" type of reaction consisting of first clonic, tonic, and second clonic phases, terminating in a state of coma.

It may be observed from these tables that the blood pressure changes in connection with metrazol treatment coincide *primarily* with the state of *emotional excitement* and *mental awareness* of the patient at the time the reading is taken. (This relationship is clearly indicated by study of the notes made in the "Remarks" column of the table.) The blood pressure changes do not appear to have any special relationship to the amount of drug injected. The type of physical reaction induced by the injection seems to influence the blood pressure only in so far as it determines to a large extent the mental and emotional state of the patient at the time the readings are taken. Thus, the figures in table A (in which are grouped the blood pressure readings before and after injections in which "stimulation only" was obtained) indicate a definite trend towards a slight elevation of systolic, diastolic, and

pulse pressure in these cases. Thus, five instances in which metrazol alone was used and "stimulation only" resulted gave an average systolic blood pressure rise of 9 mm. of mercury, with an average diastolic rise of 2.8 mm.

The figures in table B (in which are grouped the blood pressure readings before and after injections in which a "petit mal" type of reaction was obtained) indicate a definite trend towards a *moderate* elevation of systolic and diastolic pressures.

The figures in table C (in which are grouped the blood pressure readings before and after injections in which a "grand mal" type of reaction was obtained, and in which consequently the postconvulsive reading was taken in a state of more or less complete coma) indicate a definite trend towards a moderate drop in the systolic and diastolic pressures as an immediate consequence of the fit.

Blood pressures taken during the preconvulsive interval (that is, before the intravenously injected drug has had an opportunity to exert any visible effect on the nervous system) invariably show no significant change when compared with those taken before the metrazol injection (see items number 2 and 3 in table B<sub>1</sub>, and items number 8, 15, 16, 20, 21, and 23 in table C<sub>1</sub>).

Blood pressures taken in succession during the postcomatose "awakening" stage show a progressive increase which pretty well corresponds to the state of mental awareness and excitement clinically evident. (See items number 9, 7, 8, 21, 13, 16, 22 of table C<sub>1</sub>, and numbers 7, 16, 8, 20, 4 of table C<sub>2</sub>.) Blood pressures taken after the patient is again fully conscious and recovered from the fit, as well as blood pressures taken in the afternoon several hours after the fit, show no significant variation from their usual normal level.

In those instances in which the metrazol was given when the patient was in a state of hypoglycemic shock, the blood pressure changes generally were in the same direction but rather more marked in degree than in those cases in which metrazol was given alone (compare tables A<sub>2</sub> with A<sub>1</sub>, B<sub>2</sub> with B<sub>1</sub>, C<sub>2</sub> with C<sub>1</sub>). This would seem to indicate that the administration of the insulin had caused an increase in the cardiovascular lability of these patients. This finding is in accord with our concepts of the cardiovascular effects of insulin treatment, as previously reported.<sup>10</sup>

The preponderant influence of the emotional status of the patient on the extent of the blood pressure changes following the injection of metrazol is more clearly indicated when one considers only those cases in which an evident state of fear or excitement was noted at the time of the injection. Such a state was noted nine times when metrazol alone was used (table C<sub>1</sub>) and four times when metrazol was given after insulin (table C<sub>2</sub>). The readings in these instances are distinguished from the others by the placing of a "plus" sign in the last column of the blood pressure tables. The figures from table C<sub>1</sub> show that in the instances in which there was obvious fear and excitement the average systolic blood pressure change was minus 21.9 mm. as compared with a general average systolic change of minus 9.3 mm.

TABLE A  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials, Case No., Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change
A: "Stimulation only."	1	M. B. No. 6 6-6-38	5 c.c. Metrazol	162/92	170/98	Patient very fearful, apprehensive, and excited both before and after the injection	+ 8	+ 6	+ 2
	2	M. B. No. 6 6-11-38	6.2 c.c. Metrazol	132/74	140/78	Patient moderately apprehensive, but compliant to treatment	+ 8	+ 4	+ 4
	3	E. D. No. 2 6-15-38	5.2 c.c. Metrazol	134/82	140/80	126/78 (immediately after) $\rightarrow$ $\frac{140}{80}$ (1 min.) $\rightarrow$ $\frac{142}{80}$ (2 min.)	+ 6	- 2	+ 8
A <sub>1</sub> : Metrazol alone	4	E. D. No. 2 6-15-38	5.6 c.c. Metrazol	140/76	142/82	No reaction, 140/78 immediately after $\rightarrow$ $\frac{142}{82}$ (1 min.)	+ 2	+ 6	- 4
	5	H. T. No. 3 6-17-38	5.2 c.c. Metrazol	135/72	156/72	Slight stimulation only (EKG taken)	+ 21	0	+ 21
A <sub>2</sub> : Insulin and Metrazol	1	B. V. D. No. 4 5-20-38	3.8 c.c. Metrazol 120 u. Ins.	124/46	144/52	Patient drowsy prior to injection—not apprehensive	+ 20	+ 6	+ 14
	2	B. V. D. No. 4 5-25-38	5 c.c. Metrazol 120 u. Ins.	154/66	165/66	Slight stimulation only	+ 14	0	+ 14
	3	C. W. No. 13 5-25-38	3 c.c. Metrazol 30 u. Ins.	120/74	142/90	Patient in light insulin coma at time of M. injection	+ 22	+ 16	+ 6
	4	G. V. No. 11 6-6-38	4.4 c.c. Metrazol 80 u. Ins.	122/70	136/76		+ 14	+ 6	+ 8
	5	H. K. No. 12 6-9-38	3 c.c. Metrazol 15 u. Ins.	106/76	110/80	Single slight quiver	+ 4	+ 4	0

{ Range of Systolic B.P. Changes = +2 to +21; Average Syst. B.P. Change = +9  
 A<sub>1</sub> { Range of Diastolic B.P. Changes = -2 to +6; Average Diast. B.P. Change = +2.8  
 Range of Pulse Pressure Changes = -4 to +21; Average Pulse Pressure Change = +6.2  
 A<sub>2</sub> { Range of Systolic B.P. Changes = +4 to +22; Average Syst. B.P. Change = +14.8  
 Range of Diastolic B.P. Changes = 0 to +16; Average Diast. B.P. Change = +6.4  
 Range of Pulse Pressure Changes = 0 to +14; Average Pulse Pressure Change = +8.4

TABLE B  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials Case No. Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Sys-tolic B.P. Change	Dias-tolic B.P. Change	Pulse Pres-sure Change
B: "Petit Mal" B <sub>1</sub> : Metrazol alone	1	M. C. No. 7 5-25-38	12.8 c.c. Met.	150/80	162/82		+12	+ 2	+10
	2	M. C. No. 7 6-17-38	13 c.c. Met.	154/80	150/90	1st phase only—duration 45 seconds B.P. 152/88 during preconvulsive interval	- 4	+10	-14
	3	M. C. No. 7 6-21-38	13 c.c. Met.	160/90	192/100	1st phase only; 2 minutes later, quiet-162/88. B.P. 156 systoles during preconvulsive interval	+32	+10	+22
B <sub>2</sub> : Insulin and Metrazol	1	F. S. No. 8 5-20-38	8.4 c.c. Met. 120 u. Ins.	144/74	172/78		+28	+ 4	+24
	2	F. S. No. 8 5-21-38	8.6 c.c. Met. 120 u. Ins.	130/72	148/82	Marked excitement after injection	+18	+10	+ 8
	3	F. S. No. 8 6-11-38	9.4 c.c. Met. 120 u. Ins.	128/82	144/86	Prolonged 1st phase with marked excitement	+16	+ 4	+12
	4	C. P. No. 10 5-28-38	3.6 c.c. Met. 100 u. Ins.	122/70	120/72		- 2	+ 2	- 4
	5	C. P. No. 10 6-8-38	5.8 c.c. Met. 120 u. Ins.	122/0	126/0	10 minutes later = 124/76	+ 4	0	+ 4
	6	C. W. No. 13 6-8-38	4 c.c. Met. 30 u. Ins.	130/92	148/94	Struggling after injection	+18	+ 2	+16

{ Range of Systolic B.P. Changes = - 4 to +32; Average Systolic B.P. Change = +13.3  
 B<sub>1</sub> { Range of Diastolic B.P. Changes = + 2 to +10; Average Diastolic B.P. Change = + 7.3  
 { Range of Pulse Pressure Changes = -14 to +22; Average Pulse Pressure Change = + 6  
 { Range of Systolic B.P. Changes = - 2 to +28; Average Systolic B.P. Change = +16.4  
 B<sub>2</sub> { Range of Diastolic B.P. Changes = 0 to +10; Average Diastolic B.P. Change = + 4.4  
 { Range of Pulse Pressure Changes = - 4 to +24; Average Pulse Pressure Change = +12.

TABLE C1  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials, Case No., Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
C: "Grand Mal" C1: Using Metrazol only	1	M. C. No. 7 5-20-38	12.4 c.c.	148/80	190/90		+42	+10	+32	
	2	M. C. No. 7 5-28-38	13 c.c.	140/72	146/82		+6	+10	-4	
	3	M. C. No. 7 6-1-38	13 c.c.	165/86	142/68	Fearful and excited before injection	-23	-18	-5	+
	4	M. C. No. 7 6-6-38	13 c.c.	170/92	142/84	Fearful and excited before injection	-28	-8	-20	+
	5	M. C. No. 7 6-8-38	13 c.c.	164/76	128/68	Excited and struggling before injection	-36	-8	-28	+
	6	M. C. No. 7 6-11-38	13 c.c.	164/92	132/86	Very fearful before injection	-32	-6	-26	+
	7	M. C. No. 7 6-13-38	13 c.c.	150/90	138/78	B.P. 152/90 one minute later (awaking from coma)	-12	-12	0	
	8	M. C. No. 7 6-15-38	13 c.c.	154/86	144/80	B.P. 148 systolic in preconvulsive interval; B.P. 158/96 one minute after fit (awaking from coma)	-10	-6	-4	
	9	M. B. No. 6 6-8-38	6 c.c.	128/78	130/82	B.P. 152/90 one minute later (awaking from coma)	+2	+4	-2	
	10	M. B. No. 6 6-13-38	6.6 c.c.	136/76	152/96	B.P. 170/96 during late clonic phase	+16	+20	-4	
	11	M. B. No. 6 6-15-38	6.8 c.c.	152/92	136/80	Fearful and pleading before injection	-16	-12	-4	+
	12	M. B. No. 6 6-17-38	7 c.c.	138/78	118/62	Fearful and pleading before injection	-20	-16	-4	+
	13	M. B. No. 6 6-21-38	7.2 c.c.	154/90	148/62	Very fearful before injection. B.P. 172/92 two minutes later (awaking from coma)	-6	-28	+22	+
	14	M. B. No. 6 6-24-38	7.4 c.c.	146/78	138/68		-8	-10	+2	
	15	E. D. No. 2 6-13-38	5 c.c.	126/72	150/84	Systolic B.P. 130 just before convulsion began; pre-convulsive interval prolonged to 50 seconds	+24	+12	+12	

TABLE C<sub>1</sub>—Continued

Type of Reaction	Item No.	Initials Case No., Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
	16	E. D. No. 2 6-21-38	6 c.c.	140/74	140/78	Preconvulsive interval prolonged to 40 seconds; B.P. during preconvulsive interval = 136/76. B.P. two minutes after fit = 162/98 (awaking from coma)	0	+4	-4	
	17	R. M. No. 14 6-13-38	4 c.c.	148/82	150/80	Pulse quite irregular and rapid (rate 160) for first couple of minutes after fit	+2	-2	+4	
	18	R. M. No. 14 6-15-38	4.2 c.c.	162/72	140/72	Excited before injection	-22	0	-22	+
	19	R. M. No. 14 6-17-38	4.4 c.c.	152/86	148/78	EKG taken while awaking from coma (two minutes after fit)	-4	-8	+4	
	20	R. M. No. 14 6-24-38	4.8 c.c.	162/84	148/80	Fearful before injection. Systolic B.P. during preconvulsive interval = 172	-14	-4	-10	+
	21	H. T. No. 3 6-15-38	5 c.c.	136/70	90/0	Preconvulsive interval prolonged to 44 seconds; B.P. during preconvulsive interval = 140/78; Showed marked goose-flesh all over and marked perinasal pallor	-46	-70	+24	
	22	H. T. No. 3 6-21-38	6 c.c.	138/74	118/44	B.P. 1 min. after fit = 110/0 B.P. 2 min. after fit = 122/0 B.P. 4 hrs. later = 134/82 EKG taken 20 sec. after end of fit. B.P. 122/70 2 min. later (while Lead IV of EKG was being recorded)	-20	-30	+10	
	23	H. T. No. 3 6-24-38	6.2 c.c.	130/74	122/72	B.P. during preconvulsive interval = 142/90	-8	-2	-6	

Range of Systolic B.P. Changes = -46 to 42; Average Syst. B.P. Change = -9.3; Aver. Syst. Change  $\bar{c}$  "E" = -21.9.  
 Range of Diastolic B.P. Changes = -70 to +20; Average Dias. B.P. Change = -7.8; Aver. Dias. Change  $\bar{c}$  "E" = -11.1.  
 Range of Pulse Pressure Changes = -28 to +32; Average P.P. Change = -1.4; Aver. P.P. Change  $\bar{c}$  "E" = -10.8.  
 Number instances with obvious excitement = 9(+) (with excitement changes were always downward).

TABLE C II  
Effects of Metrazol on Blood Pressure

Type of Reaction	Item No.	Initials, Case No. Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
C: "Grand Mal" C: Using Insulin and Metrazol	1	G. V. No. 11 5-20-38	80 u. Ins.	124/64	132/70		+ 8	+ 6	+ 2	
	2	G. V. No. 11 5-26-38	4 c.c. Met.	112/80	110/70		- 2	- 10	+ 8	
	3	G. V. No. 11 6-1-38	4.4 c.c. Met.	124/88	112/76		- 12	- 12	0	
	4	G. V. No. 11 6-9-38	4.4 c.c. Met.	128/68	90/30	B.P. 110/56 one-half minute later—130/72 one minute later	- 38	- 38	0	
	5	G. V. No. 11 6-9-38	80 u. Ins.	182/114	132/78	Fearful before injection	- 50	- 36	- 14	+
	6	G. V. No. 11 6-9-38	4.8 c.c. Met.	118/74	98/66		- 20	- 8	- 12	
	7	G. U. No. 9 5-25-38	8.8 c.c. Met.	200/108	162/92	Fearful before injection; B.P. 202/90, 5 min. later (awaking from coma); B.P. 156/106, 25 min. later	- 38	- 16	- 22	+
	8	G. U. No. 9 5-25-38	120 u. Ins.	196/108	148/86	Fearful before injection; B.P. 160/90, 172/92, two and four minutes later (awaking from coma)	- 48	- 22	- 26	+
	9	G. U. No. 9 5-28-38	8.8 c.c. Met.	168/94	174/86		+ 6	- 8	+ 14	
	10	G. U. No. 9 6-1-38	120 u. Ins.	170/108	156/76		- 14	- 32	+ 18	
	11	G. U. No. 9 6-8-38	8.8 c.c. Met.	190/108	154/74	Fearful before injection	- 36	- 34	- 4	+
	12	C. P. No. 10 5-20-38	120 u. Ins.	122/78	138/78		+ 16	0	+ 16	
	13	C. P. No. 10 6-1-38	3.6 c.c. Met.	112/72	118/76		+ 6	+ 4	+ 2	
	14	C. P. No. 10 6-6-38	100 u. Ins.	122/68	126/68		+ 4	0	+ 4	
	15	C. P. No. 10 6-9-38	4 c.c. Met.	124/0	114/42		- 10	+ 42	- 52	
	16	B. V. D. No. 4 5-21-38	100 u. Ins.	138/52	110/40	B.P. 160/54 two min. later (post convulsive confused excitement developing); B.P. 174/44 four minutes later; B.P. 136/60 thirty minutes later (awake, calm, reading newspaper)	- 28	- 12	- 16	

TABLE C II—Continued

Type of Reaction	Item No.	Initials, Case No. Date	Dose of Medication	B.P. before Injection	B.P. after Injection	Remarks	Systolic B.P. Change	Diastolic B.P. Change	Pulse Pressure Change	Cases Showing Obvious Excitement before Injection
	17	B. V. D. No. 4 5-26-38	120 u. Ins. 5.4 c.c. Met.	128/66	150/48		+22	-18	+40	
	18	B. V. D. No. 4 5-28-38	120 u. Ins. 5.4 c.c. Met.	126/66	120/52		-6	-14	+8	
	19	B. V. D. No. 4 6-1-38	120 u. Ins. 5.4 c.c. Met.	138/60	130/50		+8	+10	-2	
	20	B. V. D. No. 4 6-6-38	120 u. Ins. 5.8 c.c. Met.	148/46	150/12	B.P. 172/40 one minute later (beginning to awake from deep coma)	+2	-34	+36	
	21	B. V. D. No. 4 6-8-38	120 u. Ins. 3.2 c.c. Met.	136/72	116/0		-20	-72	+52	
	22	B. V. D. No. 4 6-11-38	120 u. Ins. 5.8 c.c. Met.	116/50	96/28		-20	-22	+2	
	23	C. W. No. 13 5-21-38	30 u. Ins. 3 c.c. Met.	140/94	132/80		-8	-14	+6	
	24	C. W. No. 13 5-26-38	35 u. Ins. 3.2 c.c. Met.	112/68	116/66		+4	-2	+6	
	25	C. W. No. 13 5-28-38	30 u. Ins. 3.2 c.c. Met.	128/76	132/82		+4	+6	-2	
	26	C. W. No. 13 6-1-38	30 u. Ins. 3.2 c.c. Met.	118/76	126/72		+8	-4	+12	
	27	C. W. No. 13 6-6-38	30 u. Ins. 3.2 c.c. Met.	132/88	150/70		+18	-18	+36	
	28	C. W. No. 13 6-9-38	30 u. Ins. 3.4 c.c. Met.	122/78	120/72		-2	-6	+4	
	29	F. S. No. 8 5-25-38	140 u. Ins. 9 c.c. Met.	122/78	122/68		0	-10	+10	
	30	H. K. No. 12 6-11-38	15 u. Ins. 3.4 c.c. Met.	112/84	120/72		+8	-12	+20	

Range of Systolic B.P. Changes = -50 to +22; Average Syst. B.P. Change = -7.6; Average Syst. Change  $\bar{c}$  Excitement = -43.  
 Range of Diastolic B.P. Changes = -36 to +42; Average Diast. B.P. Change = -12.9; Average Diast. Change  $\bar{c}$  Excitement = -27.  
 Range of Pulse Pressure Changes = -52 to +52; Average Pulse Pressure Change = +4.9; Average P.P. Change  $\bar{c}$  Excitement = -16.5.  
 Number instances with obvious excitement = 4(+) (with excitement changes were always downward).

TABLE D  
EKG Effects of Metrazol

STATISTICAL DATA	Item No.	1	2	3	4	5						
	Case No. Date of EKG	No. 1 W. B. 3-11-38	No. 2 E. D. 3-11-38	No. 4 B. V. D. 3-8-38	No. 5 W. C. 3-7-38	No. 6 M. B. 3-2-38						
	Age of patient	46	41	26	41	38						
	No. of previous metrazol treatments and fits	25 treatments 18 fits	25 treatments 14 fits	23 treatments 10 fits	7 treatments 4 fits	1 treatment 1 fit						
	Dose of met. on date of EKG	10.2 c.c.	10.8 c.c.	12.6 c.c.	7 c.c.	4 c.c.						
EKG Data: taken: (A) immediately before, and (B) within 10 minutes after Metrazol convulsion	EKG data	Before	After	Before	After	Before	After					
	Rate	111	122	107	103	97	110	83	107	91	115	
	Rhythm	Regular	Regular	Regular	† Grossly regular	Regular	Regular	Regular	Regular	Regular	Regular	
	Duration of com- plexes (seconds)	P	.08	.08	.10	.10	.11	.11	.09	.09	.10	.10
		PR	.12	.12	.20	.19	.17	.17	.14	.14	.18	.18
QRS		.09	.09	.09	.10	.08	.08	.10	.10	.08	.08	
ST		.22	.20	.24	.26	.24	.20	.24	.22	.22	.24	

TABLE D—Continued

Cardiac apex to left leg	LEAD IV	Amplitude of waves (in millimeters)									
		LEAD I	P <sub>1</sub> Q <sub>1</sub> R <sub>1</sub> S <sub>1</sub> T <sub>1</sub>	+1½ -1 +8 - +1	+1 - +2 -2 +1	+½ - +2 -3 +1	+1 - +5 -2 +1½	+1 -1 +6½ - +1	+1 -1½ +8 - +1½	+1 -3½ +10½ - +1	+½ - +5 -1 +½
(A) immediately before, (B) within 10 minutes after Metrazol convulsion	LEAD II	P <sub>2</sub> Q <sub>2</sub> R <sub>2</sub> S <sub>2</sub> T <sub>2</sub>	+1½ -1½ +13 -2½ +2	+1½ -1½ +13 -2½ +2	+2 -1½ +14 -2 +2½	+2 -1 +12 -2 +1½	+2 -2 +13 -2 +1½	+1½ -2½ +13 - +2	+1½ -3½ +16 - +1 1/2	+1½ - +12 -3 +1½	+2 - +12 -3 +2½
	LEAD III	P <sub>3</sub> Q <sub>3</sub> R <sub>3</sub> S <sub>3</sub> T <sub>3</sub>	+1½ -1 +13 -1 +½	+1 -1 +13 -1 +½	+1½ -2 +17 -½ +1½	+1 -½ +6 -1 Flat	+1 -8 +2 -2 Flat	Flat - +7 - +½	+1 - +9 - +1	+1 - +7 -2 +1	+1½ - +6½ -1½ +1½
			Nothing abnormal	Nothing abnormal	Nothing abnormal	Nothing recorded	Nothing abnormal	Not recorded	Not recorded	Nothing abnormal	Nothing abnormal

\* Occasional auricular extrasystoles after the fit. T<sub>4</sub> is -4 mm. or 2 mm. deeper after fit than before fit.  
 † Occasional auricular and ventricular (left) extrasystoles are seen after the fit; T<sub>4</sub> is -4 mm. or 2 mm. deeper after fit than before.

TABLE D—Continued  
EKG Effects of Metrazol

STATISTICAL DATA	Item No.	6	7	8	9	10					
	Case No. Date of EKG	No. 7 M. C. 3-2-38	No. 3 H. T. 3-7-38	No. 3 H. T. 6-17-38	No. 3 H. T. 6-21-38	No. 14 R. M. 6-17-38					
	Age of patient	42	42	42	42	39					
	No. of previous metrazol treatments and fits	1 treatment 1 fit	23 treatments 16 fits	30 treatments 22 fits	32 treatments 23 fits	31 treatments 28 fits					
	Dose of met. on date of EKG	5 c.c.	9.6 c.c.	5.2 c.c.	6 c.c.	4.4 c.c.					
EKG DATA: taken: (A) immediately before, 10 minutes after Metrazol convulsion	EKG data	Before	After	Before	After	Before	After				
	Rate	75	83	100	115	94	115	147	103	145	
	Rhythm	Regular	Regular	Regular	Regular	Regular	Sl. sinus arrhyth.	Regular	Regular	Regular	
	Duration of com-plexes (seconds)	P	.08	.09	.09	.09	.09	.09	.09	.08	.08
		PR	.15	.16	.13	.13	.14	.14	.14	.12	.12
	QRS	.09	.09	.06	.07	.06	.07	.07	.06	.06	
	ST	.26	.24	.28	.24	.28	.24	.22	.26	.24	

TABLE D—Continued

Cardiac apex to left leg	Remarks	Amplitude of waves (in millimeters)									
		LEAD I		LEAD II		LEAD III		LEAD IV		Nothing abnormal	
EKG DATA: taken: (A) immediately before, (and) (B) within 10 minutes after Metrazol convulsion		P <sub>1</sub> Q <sub>1</sub> R <sub>1</sub> S <sub>1</sub> T <sub>1</sub>	+ - +7 -2½ +1½	+1 -1 +8 -2 +2½	+ - +3 -1 Flat	Unsat- isfactory graph (muscle currents)	+ - +2 -1 +½	+ - +2 -1 +½	+ - +2 -1 +½	+ - +2 -1 +½	+ - +2 -1 +½
		P <sub>2</sub> Q <sub>2</sub> R <sub>2</sub> S <sub>2</sub> T <sub>2</sub>	+1 -1 +9 -3 +2	+1½ -1 +8 -3 +3	+2 -2 +10 -1 +1	+2 -2 +9 -2 +1½	+1½ -1 +6 -1 +1½	+1 -1 +7 -1 +1	+1 -1 +2 -1 +2	+1 -1 +7 -1 +2	+1 -1 +10 -1 +2
		P <sub>3</sub> Q <sub>3</sub> R <sub>3</sub> S <sub>3</sub> T <sub>3</sub>	+ - +2½ -1 +1	+1 -1 +1 -1 +1½	+1½ -1 +7 -1 +1	+1½ -1 +7 -1 +1	+1 -1 +4 -1 +1	+1 -1 +4 -1 +1	+1½ -1 +5 -1 +1½	+1 -1 +5 -1 +1	+1 -1 +7 -1 +1
			Nothing abnormal	Nothing abnormal	Not recorded	T <sub>4</sub> neg. shallow (-1 mm.)	T <sub>4</sub> diphasic -1/2 to +1/2 mm.	T <sub>4</sub> shallow (-½ mm.)	T <sub>4</sub> equals -2 mm.	Nothing abnormal	Nothing abnormal
				T <sub>4</sub> is -4 as compared to -3 mm. before fit		B.P. 135/72	Slight stimulation only B.P. 156/72	B.P. 138/74	B.P. 118/44	B.P. 152/86	B.P. 148/78

\* Occasional auricular extrasystoles after the fit.  $T_4$  is -4 mm, or 2 mm, deeper after fit than before fit.  
† Occasional auricular and ventricular (left) extrasystoles are seen after the fit;  $T_4$  is -4 mm, or 2 mm, deeper after fit than before.

Similar differences are apparent as regards the diastolic and pulse pressure changes, and a similar, but even more marked trend, is discernible in table C<sub>2</sub> where the "metrazol with insulin" cases are listed.

The readings listed as item number 21 in table C<sub>1</sub> merit some special consideration. This patient, after this particular injection showed a drop of his diastolic blood pressure to zero, which persisted for several minutes. This is evidence of the appearance consequent to the seizure, of an adrenalin or adrenalin-mimetic effect, which is entirely similar to the adrenalin effect often obtained during insulin hypoglycemia. (This phenomenon has been fully described in our earlier paper<sup>10</sup>; its appearance as an effect of insulin hypoglycemia alone is illustrated by item number 15, in table C<sub>2</sub> and item number 5 in table B<sub>2</sub>.) This finding may be considered as confirmatory of our previous notations of the appearance of the aortic dilatation phenomena as described under the auscultatory findings. Additional evidence for such an interpretation of these findings will be presented in connection with the electrocardiographic studies. It must be reëmphasized that such evidences of adrenalin or adrenalin-mimetic cardiovascular activity were seen much less frequently and to a considerably lesser degree after metrazol injections than during insulin hypoglycemias. Patient H. T., on whom the readings listed as item number 21 were made, was one of those who had been particularly prone to exhibit the adrenalin-activity phenomena during his previous course of straight insulin treatment.

## II. ELECTROCARDIOGRAPHIC FINDINGS

Electrocardiograms were taken on eight of our more coöperative patients just before a metrazol injection and as soon as practical thereafter. This was done in 10 instances, in nine of which the desired result of a grand mal convulsion was obtained, while in one instance (item number 8) "slight stimulation only" was obtained. In the nine instances where a grand mal convulsion was obtained, the second electrocardiogram was taken as soon as possible after the last convulsive twitch, during the phase of postconvulsive coma. In the one instance where no convulsion was obtained, the second electrocardiogram was taken one and one-half minutes after the metrazol injection.

All of these patients had had electrocardiograms taken before the course of treatment was started as well as after it was finished. In addition, several of them had additional electrocardiograms taken during the afternoon or on rest days during the course of treatment. These data need not be presented here, because in no instance did there appear the slightest significant change, or evidence of cardiac damage as a result of the course of treatment. The temporary immediate changes contingent upon the individual metrazol injections are herewith presented in table D.

Analysis of the data listed in table D shows that there was no significant variation in the reaction in relation to the total number of treatments, or number of previous convulsions. The changes in rate were usually minor in

degree and confirmed the impressions previously noted by counting the pulse. In only two of the 10 instances (items number 9 and 10) did an acceleration of pulse of 32 to 42 per minute appear. The rhythm generally remained grossly regular after the fit—in one instance a slight sinus arrhythmia was noted, while in two cases occasional auricular extrasystoles appeared, and in one case rare ventricular extrasystoles were seen. There were absolutely no significant changes noted in the duration of the individual wave complexes. No significant variations were noted in the amplitude of the P, Q, R, or S waves, in any lead, except such slight increases in amplitude of the QRS complexes in two instances as might indicate a rather more vigorous ventricular action (see items number 4 and 10).

In no instances was there noted any significant deflection of the ST interval. The "T" waves generally showed either *no change* or a *slight increase* in amplitude ranging from  $\frac{1}{2}$  to 2 millimeters. This increase was generally in the direction of normality, so that  $T_1$ ,  $T_2$ , and  $T_3$  which are normally positive tended to become *more* positive, whereas  $T_4$  which is normally negative tended to become *more* negative. The change in the "T" waves was particularly evident in Lead IV (see items number 1, 2, 7, 9).

The only exceptions to this rule regarding the "T" wave changes are seen under items number 3, 4, and 8. Here we find "T" waves after the fit, which are slightly *diminished* in amplitude ( $-\frac{1}{2}$  millimeter) so that they may be considered *less* normal than before. The three cases on whom these graphs were taken were outstanding examples of those showing a special susceptibility of the cardiovascular apparatus to adrenalin or adrenalin-mimetic sympathetic activity as evidenced by aortic-dilatation phenomena, increased pulse pressure, vasomotor and pilomotor activity, when they had previously been treated with insulin.

#### DISCUSSION

In seeking an explanation for the exceptional findings noted in a few instances above we are inevitably led to a consideration of the more recent literature regarding the physiology of epinephrine, at least as it affects the heart. In this regard Milles and Smith<sup>11</sup> have stated in substance: The intravenous injection of epinephrine causes electrocardiographic changes closely simulating those found in angina pectoris in which condition the myocardium but not the conduction mechanism is involved. A *wide variation* exists in the individual *susceptibility to the drug* in humans and in experimental animals. *The minimal effect is a reduction in amplitude of the "T" wave.* This is closely followed by the appearance of the diphasic form. Next directional changes in the T-wave appear, i.e., a previously upright T-wave becomes inverted or vice versa, or a marked increase in the voltage of the T-wave appears. Deviation of the ST interval is often associated with these pronounced T-wave changes. Finally ventricular extrasystoles and, with very large doses, ventricular fibrillation set in. With very large doses of epinephrine transient conduction interference may occur.

The work of Parade and Foerster<sup>12</sup> affords additional pertinent information as to the effect of epinephrine on the heart action. These investigators administered 0.015 mg. of a freshly prepared epinephrine solution intravenously to a series of 35 non-cardiac patients. They then took serial electrocardiograms in Lead II only, and in 18 cases observed definite rhythm changes which, however, always subsided within 5 minutes after the injection. The rhythm changes were divided as follows: nodal rhythm—five times; coronary vein sinus rhythm (an ectopic auricular rhythm)—two times; nodal extrasystoles—three times; auricular extrasystoles—four times; ventricular extrasystoles—three times. They also observed occasionally a slight sinus arrhythmia which was not due to respiration. In two cases they found rather long maintained deformities of the P-wave. In one patient there occurred an heterotopic auricular tachycardia. In almost half of their cases there occurred a slight fleeting shortening of the PR interval.

When we add to the above data our knowledge of the infrequently mentioned and rarely recognized clinical cardiovascular effects of hyperadrenalinemia (see number 10), namely the aortic dilatation phenomena, we find that we are able to formulate a reasonable hypothesis which will account for all the diverse clinical data disclosed by our study. First, we must recognize that individuals differ in the organization of their autonomic nervous system. This difference in autonomic organization is a most important factor of their general physical constitution or habitus. Consequently, they will differ in their response to various types of stimuli and, in the present connection, particularly in the degree of their response to drugs of the sympathetic-adrenal type. In other words, some individuals will show an increased, some a reduced, and some an "average" susceptibility or sensitivity to stimulation with adrenalin or sympathetico-mimetic drugs. Furthermore, it is now being recognized that the prolonged administration of insulin (as in the Sakel regime), may induce an altered state of reactivity of the sympathetic system, primarily in the direction of an increased sensitivity of response to adrenalin and sympathetico-mimetic drugs. On individuals with an "average" or "reduced" sensitivity of the sympathetic nervous system, it appears that metrazol, as at present employed, produces only minor cardiovascular effects, which effects correspond basically with the state of mental or emotional excitement produced by the action of the drug on the central nervous system. On the other hand, on patients with a hypersensitivity of the sympathetic nervous system, metrazol may produce, in addition, transitory effects which are typical of a mild hyperadrenalinemia, namely, aortic dilatation phenomena with reduced diastolic and increased pulse pressures, cardiac rhythm changes, and T-wave changes (such as were noted with patients H. T., W. C., and B. V. D.).

From the above formulation it follows that metrazol may logically be employed with safety in all cases which do not show definite evidence of serious organic heart disease. In cases of definite organic heart disease its use would seem to be contraindicated, when the disease is of a type which

tends towards permanent disturbances of rhythm (such as rheumatic, thyrotoxic, or advanced arteriosclerotic conditions), or of a type associated with defective coronary function (such as coronary sclerosis, or aortic regurgitation). In such cases, in sensitive or sensitized individuals, an injection of metrazol might conceivably induce sufficient additional sympathetic stimulation (or adrenalin secretion), to precipitate a cardiac accident. On the whole it appears that metrazol may be employed with a feeling of much greater assurance in borderline cardiac cases than would be the case with insulin, which, it has been shown, produces much more profound and more lasting changes in the cardiovascular physiologic processes.

Corresponding with the evident safety of metrazol as regards the cardiovascular apparatus, there appears to be no good evidence of its possessing any real value as a pure cardiac stimulant. It would seem that whatever good effects may be obtained from its use as a cardiac stimulant could best be explained by its pronounced respiratory stimulant action, with perhaps secondary improvement of cardiac function due to improved oxygenation.

#### SUMMARY

The present vogue of using massive doses of metrazol intravenously for the treatment of mental diseases, has afforded an unprecedented opportunity for studying directly the effects of this drug on the cardiovascular physiologic processes.

A survey of the current literature shows that there have been published comparatively few reports furnishing any specific data on this problem.

The present study lists changes in the physical signs, blood pressure, and electrocardiograms of 14 male patients receiving metrazol alone, as well as metrazol during the course of insulin hypoglycemia. It is indicated that there are no pronounced or prolonged alterations in blood pressure associated with the metrazol treatment per se, and that the changes which do occur reflect primarily the state of mental and emotional excitement or depression induced by the injection. It is also shown that the metrazol injections as a rule induce a *transitory* mild to moderate acceleration of cardiac rate (10 to 30 beats per minute), and at times *transitory cardiac irregularities* most often of the type of auricular extrasystoles, and sinus arrhythmia, with ventricular extrasystoles more rarely. We have not observed any instance of auricular fibrillation, although this has been reported by another investigator (Haddorn). It is also shown that patients who are "sensitive" or "have been sensitized" (by previous treatment with insulin) may show temporary signs of aortic dilatation phenomena, analogous to the known effects of a mild hyper-adrenalinemia. Except in such "sensitized" patients, where the electrocardiograms may indicate a slight tendency towards diminished coronary oxygenation, the electrocardiograms after convulsions invariably indicate either no change or improved coronary oxygenation, associated with the more vigorous heart action. The theoretical implications of these findings

are suggested and the relative safety of metrazol treatment as regards improbability of cardiac complications is stressed.

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## ACTINOMYCOSIS: A NEW SPECIES, PATHOGENIC FOR MAN \*

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THE diagnosis of human actinomycosis is not always made with ease, and furthermore the identification of the causative species is usually quite difficult. In medical literature cases are frequently reported as actinomycosis followed by the statement, *unable to culture, culture lost, not able to identify*, etc. The species in some cases is not of great interest to the physician; however, the laboratory should always attempt to identify the organism.

The disease may be either localized or generalized. It is usually chronic and the duration is from several months to several years. It is thus frequently misdiagnosed "tuberculosis."

In 1925, Sanford and Voelker<sup>1</sup> reviewed 670 cases that had been observed up to that year in the United States, and of these only 2 per cent showed generalized involvement. Brumpt states that in those infections caused by *A. israeli*, the etiological agent of lumpy jaw in cattle, 60 per cent of the cases are of the cervico-facial type. When all causative species are grouped together this percentage is much greater. In certain cases decaying teeth may contain the organism and as such may be the source of the infection. Topley and Wilson<sup>2</sup> state that *A. graminis Bostroem* is occasionally present in actinomycotic lesions and is probably not etiologically related to the disease. This organism, like the one herein later described, has been found in the mouth.

Some of the many difficulties and peculiarities encountered in the study of the group are: (1) their minute size and variation in morphology on various media; the difficulty of studying the morphology unless the highest magnifications are available, that is about 2700; (2) extreme variability of growth on synthetic media; (3) uniformity of growth on protein media; (4) the presence or absence of diffusible pigments, the colors of which may change with a variation in the pH; (5) sensitivity to an acid medium; (6) formation of zones of peculiar designs on media; (7) possible loss, after several transplants, of some of the characteristics by which they are identified. (Some of these characteristics may be regained by cultivation in media containing sterile soil, for the original source of this fungus is the soil.)

There are many species more or less pathogenic to man and animals. Brumpt<sup>3</sup> lists over one hundred. Dodge<sup>4</sup> lists about the same number. In many, pathogenicity has not been proved. Different species have been isolated from infections of the tear ducts, cornea, conjunctiva and tongue. They have been found in decaying teeth, in the sputum, in the lungs, in the spleen, and in chronic abscesses in various parts of the body. Other species

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† Deceased.

have been frequently reported in chronic bronchitis and also as associated with the tubercle bacillus in the sputum. In rarer instances we find actinomyces reported in brain abscesses, granulomas, skin mycosis, keratolysis of the skin of the feet in India, and in the blood stream of persons bitten by certain small wild animals. It is well known that several species are the etiological agents of Mycetoma or Madura foot. Generalized actinomycosis caused by the *Actinomyces bovis* of Hartz has been extensively studied by several investigators. The physician's knowledge of the disease and the organism has been largely limited to this species.

#### CASE REPORT

*Clinical History:* V. B., white male, aged 41 years, was first seen December 21, 1935, when he complained of dental pain in the lower right jaw. Examination at the Dental Clinic, Fort Leavenworth, Kansas, showed caries with periapical abscess of



FIG. 1. The lesion.

the right lower, first and second molars, pulpitis of the left lower second bicuspid and periodontoclasia of the left lower second molar. The abscesses were drained, and a few days later fluctuation appeared midway along the lower line of the right mandible. This was excised and drained. The two abscessed teeth were removed on January 3 and 6. The wound in the gum healed readily but the external wound would not close; fluctuation would again start in an adjacent indurated area. When the latter area was incised and drained, it would close and the process would begin anew.

The patient was admitted to the Station Hospital, Fort Leavenworth, on February 17, 1936, two months after the first complaint, that of dental pain. He was admitted for treatment of the abscessed area of the right lower jaw, which had become quite extensive and had become tender to light pressure.

*General Physical Examination:* This was essentially negative and remained so throughout his stay in the hospital.

*Progress in the Hospital:* The temperature was normal and remained so during the entire course of the illness. The wound was kept widely opened, and was packed



FIG. 2a. Dental—right first and second molars.  
2b. Dental—left first molar.

and dressed daily. The pus was a thick yellow but it became thin and watery as the wound closed, only to indurate again and break down repeatedly, as it had done prior to admission. The cervical glands were not enlarged. Fungus infection had been suspected by the surgeon for some time, but the laboratory findings were always negative, i.e., the bi-polar staining bacillary forms were not recognized as fungus. Potassium iodide was begun on March 2, a week before fungus was reported. The initial dose of 10 drops of saturated solution t.i.d. was gradually increased to 78 drops t.i.d. In addition roentgen-ray treatment was given once weekly. The wound showed much stubbornness in healing, but it finally cleared up completely except for a considerable amount of scarring. The patient was discharged on May 16, 1936.

*Laboratory Findings during Time the Patient Was in the Hospital:* On February 20, smears from the discharge were reported to contain diphtheroid-like bacilli, streptococcus and staphylococcus. Repeated cultures taken during the next two weeks continued to show the same organisms. The roentgen-ray report was negative for osteomyelitis. Blood culture taken February 19 was negative. On March 9, thread-like fungi were reported in smears, for the first time. They were aerobic, gram-positive and not acid fast. The same organism was reported on March 18 and 19. In the pus were noted minute, pale yellow, soft granules. These when crushed and stained showed colonies of actinomyces.

*Histopathology:* Tissue from the wound was sent to the Army Medical School. The report received March 15 was "chronic inflammation and small coccoid forms." Six guinea pigs were inoculated intraperitoneally with both exudate and broth cultures. In 10 days all showed small nodules at the site of inoculation. At the end of four weeks, in two of the animals nodules were found in the peritoneum and omentum. Actinomyces of the same type as herein described were cultured therefrom. In our work we were unable to confirm this finding. The remaining four pigs were kept for two more months, during which time they appeared normal.

On April 3, smears and cultures were finally diagnosed as *Actinomyces*, probably *graminis*. On April 10, pus from the jaw wound showed a few branching fungi on smear and in culture. There were many negative reports between February 17 and April 10. Blood count: On only one occasion, March 13, was this abnormal: white

cells 14,700 with 70 per cent polymorphonuclear cells. Red count and differential normal. Wassermann and Kahn reactions negative. Cultures were not taken from the teeth because they were removed before the actinomyces was suspected, and before the patient had been admitted to the hospital.

COMMENT: In this case of localized actinomycosis we wish to call attention to the following points:

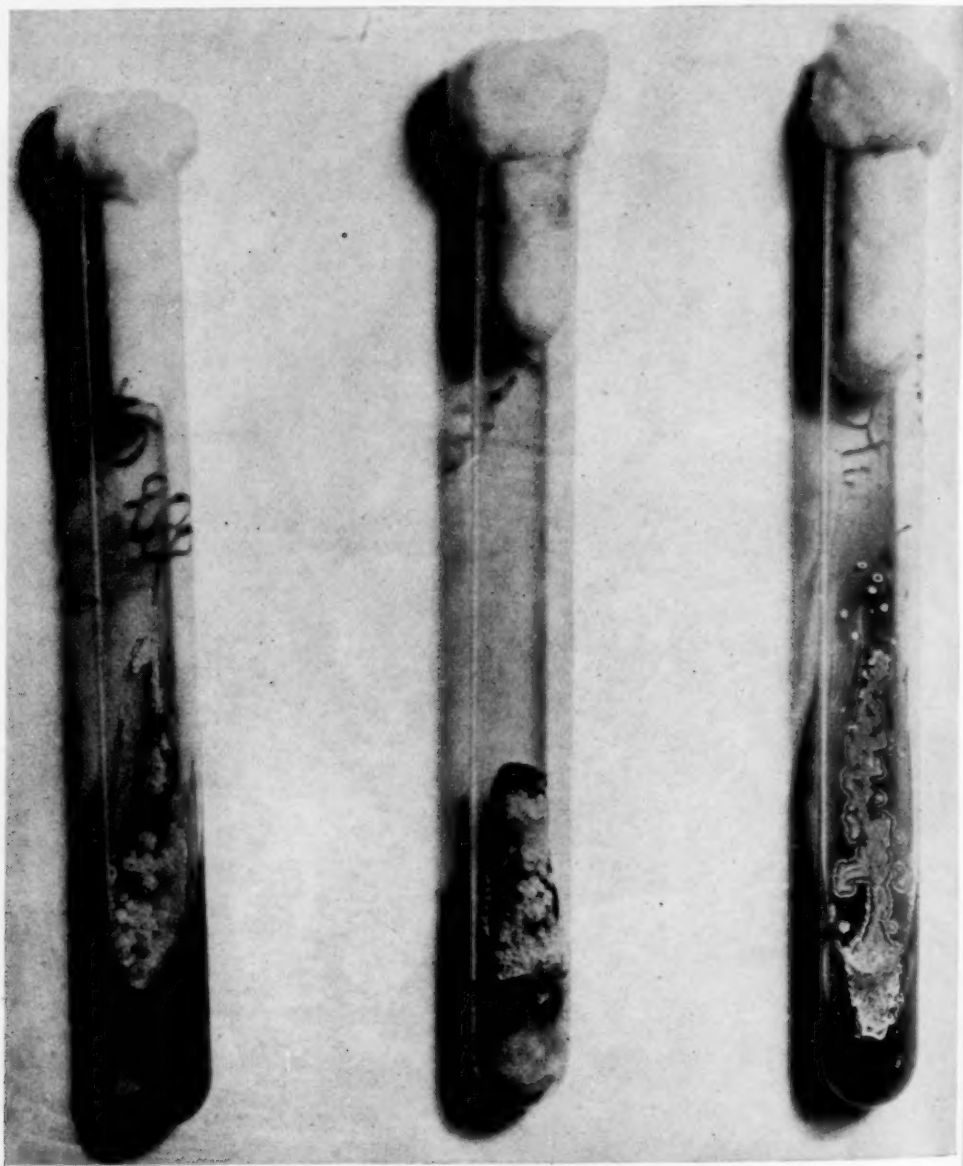


FIG. 3. The cultures showing interesting designs which may be characteristic. Left: asparagus, twelfth day. Middle: potato, twelfth day. Right: starch, twelfth day.

1. The abscess was not along a definite chain of glands as in tuberculosis.

2. Actinomycosis should always be suspected, especially in the cervicofacial area, when an abscess refuses to heal under appropriate local treatment, and the complement fixation and tuberculin tests are negative.

3. It is probable that had the organism invaded the blood stream abscesses would have occurred elsewhere and the disease might have become generalized.

4. A few weeks' delay in diagnosis may be fatal.

5. In the tissue and cultures various species of actinomyces may show coccoid, rod forms, and diphtheroid-like forms.

6. In the pus, sulphur-like granules are not always found. The same holds true for the material from the curettage of a sinus. All species do not show these granules which are characteristic of *Actinomyces bovis*.

7. The adjacent glands may not be involved.

8. The condition may be confused with tuberculosis and osteomyelitis.

9. The importance of an early localized actinomycotic infection should not be overlooked. It may become generalized.

10. Cultures should be studied for at least four weeks to determine if segmentation is present. It is often necessary to make a prolonged search for branching forms.

#### DESCRIPTION OF THE ORGANISM

Shortly after the writer came to this laboratory in May 1937, he found cultures of this actinomyces. The clinical technician, Miss Pearl Moorman, who had first recognized the filaments, described the case in such an interesting way that it was decided to attempt an identification.

On October 24, 1937, the following aerobic protein cultures were planted from old cultures dated May 18, 1936. These blood agar slants appeared to be about 70 per cent dried out. Transplants were made from a few whitish specks on the surface but were not successful. However, after admitting air the chalky white specks increased in number, and growth was obtained. The following protein and vegetable cultures were incubated at 36° C. for six days—then maintained at 18° to 22° C.

1. Rabbit blood agar slants. Period at 36° C. In 48 hours the slant was covered with heaped up, chalk-like, white, dry, finely wrinkled, confluent colonies. Hemolysis extended 10 mm. from the edge of the confluent colonies and 2 to 3 mm. from the edge of individual colonies. A similar transplant made at the same time on the same medium showed in 48 hours at 36° C. a number of discrete grayish white, glistening caput-like colonies, 4 by 4 mm., with distinct fimbriated borders which in 76 hours were covered with the same chalky substance as noted in the first transplant, and hemolysis of the slant was nearly complete. Fifth day: Growth rapid, abundant, elevated, confluent, dry, chalky with distinct contour lines, some

roundish, others squarish (see photographs). The margin was narrow, crenated and transparent in places. Growth was attached to the medium but the whitish substance was easily detached. Hemolysis was almost complete, butt excepted. One of the blood agar slants did not show the contour lines distinctly. Thirtieth day: Color had gradually changed to grayish white. Contour lines remained. Edge was lobate with shrinkage in the center of growth and the surface finely pitted, but still remained dry and powdery. Short aerial mycelium, no soluble pigment.

2. Glycerol agar slant: pH 7.2. Good rapid growth similar to above. Pattern not as distinct, more pitting of surface which is velvety and glistening with edge erose.

3. Glucose agar shake: Growth only on surface with faint blackish brown coloration a few millimeters below the surface. It is probable that this color is due to the oxidation of the glucose.

4. Glucose agar slant: Good growth, similar to number two above, but with blackish brown color diffusing into medium for a few millimeters as in number three above.

5. Loeffler slant: Rapid liquefaction which began in 40 hours and continued to about 50 per cent on the fifth day.

6. Glycerol egg slant: Liquefaction rapid.

7. Litmus milk: No typical acid coagulation. A soft jelly-like thickening with liquefaction beginning on the third day. Remained alkaline. In 10 days 60 per cent digestion.

8. Sabouraud's conservation agar: Growth similar to other solid media but not as heavy.

9. Nutrient broth, pH 6.8: Pellicle and bottom growth heavy on fifth day. Medium clear. Growth flaky, membranous and granular, depending on position in the tube. Growth up around sides of the tube above the surface. Mycelium and coccoid forms.

10. Plain agar slant: Abundant rapid growth, similar to other solid media. On filling tube with water the appearance of growth is that of a shining silver-like molten metal. No pigment. Short aerial mycelium.

11. Sabouraud slant, 4 per cent maltose, pH 6.2: Abundant and rapidly growing confluent growth, raised, buff colored, dull, coarse white granules over part of surface. Contoured border distinct and crenated with whitish stellate projections. Reverse brownish black, burnt sugar color.

12. Carrot slant: Good confluent growth. Color whitish with areas of dirty yellowish brown, mottled by a darker brown along sides of surface growth.

13. Glycerol potato slant: Growth rapid. Second day: Thin yellowish growth, borders white becoming heavy grayish white and yellow. In 10 days, heavy incrustations of chalky white substance which after 30 days becomes grayish and somewhat greenish at the base where in contact with glycerol cotton plug. Spore-like and diphtheroid-like forms. Short mycelium grows readily from the surface.

14. Gelatin: Rapid stratiform liquefaction. Synthetic media. Incubated at 36° C. for 24 hours, then maintained at 27° C.

15. Asparagin slant: Fourth day: Heavy grayish white growth on surface. Border fine and fuzzy. No diffusing pigment. Seventh day: More yellowish and drier. A few individual colonies, 2 mm. in diameter with an acuminate center growth pitted and circumscribed by a fine line of growth, a Saturnine-like ring with a clear space within. Many fine white, dust-like particles. Border finely fuzzy. Reverse a faint greenish yellow.

16. Citrate agar slant: Fourth day: Very faint colorless growth along streak. Seventh day: A dozen white powdery points less than 1 mm. in diameter. No pigment. Growth poor.

17. Starch slant with brom-cresol purple: Fourth day: Similar to asparagin but not as heavy. Seventh day: No reverse color, no liquefaction, no pigment. Growth more rapid, becoming confluent and taking on a pattern (see photographs). Short aerial mycelium. Very faint change in reaction.

18. Czapek agar slant: Fourth day: Acuminate white colonies, black speckled along streak, fir tree-like. No pigment, does not spread into medium. Aerial mycelium not noted. In 10 days many minute colonies fusing here and there. In the synthetic media no further change other than increase in growth noted between seventh and fifteenth days.

*Biochemical Characteristics:* Glucose, maltose, lactose, salicin, seven days, no change. Indol, methyl red, V.P., methyl blue reduction test, all negative. Nitrates reduced to nitrites.  $\text{NH}_3$  positive; catalase positive, rapid. Microscopic: Branched filaments about one micron in diameter, some of which contain many granules in terminal elements, probably spores. No spirals seen. Chalky surface growth is made up largely of spore-like forms, 1 or 2 microns in size which appear in short chains like streptococcus. Microcultures of these develop hyphae over night. Gram positive, not acid fast.

*Animal Inoculations:* A guinea pig and a rabbit were inoculated intraperitoneally and two similar animals subcutaneously with 1 c.c. of culture suspension. None of them lost weight or presented any abnormal signs at any time. At five weeks the first two above mentioned were opened and no pathological condition found. The remaining two are healthy and gaining weight. Actinomyces as a rule are not very pathogenic for laboratory animals.

#### DISCUSSION

After many months of work we are not able to correlate this organism with any known species. Knowing that some actinomyces change their characteristics on repeated subculture, we were careful to note that this species has retained all of its original properties, as far as we can determine from the records available. The works of various authors as Bergey,<sup>5</sup>

Topley and Wilson,<sup>6</sup> Dodge,<sup>7</sup> Brumpt,<sup>8</sup> and Waksman<sup>9</sup> have been consulted. We have written others but they have been unable to assist us. Waksman, in a personal communication, after a study of the culture sent him, says it "corresponds very closely to *A. hominis* Bostroem, which is the same as *A. gramineae*, Topley and Wilson." However, he does state that the proteolytic and diastatic properties of our organism differ from the above. The following table will show the different characters of the two species:

Media	<i>A. graminis</i>	<i>Actinomyces</i> sp. nov.
Gelatine	Liquefaction unusual.	Rapid liquefaction.
Broth	Pinkish, yellowish or orange in color. No odor.	None but chalky white. Odor distinctive.
Glucose agar slant	At three weeks, brick red or yellowish orange.	No such color. Blackish color below surface diffusing a few millimeters into medium.
Loeffler's serum	No liquefaction 24 days.	Rapid liquefaction.
Egg slant	No liquefaction 24 days.	Rapid liquefaction.
Blood agar slant	No hemolysin (Topley and Wilson). Hemolytic zone (Waksman).	Rapid and early hemolysis.
Czapek agar	Becoming yellow and brown as it dries. Penetrates the medium.	Fine white, black speckled colonies along streak. Does not penetrate into medium. Later brownish.
Starch	Enzymatic zone 12-16 mm.	No enzymatic action.
Odor	None mentioned.	Heavy penetrating, moldy, escaping through tube plugs.

This comparative table shows beyond a doubt that on a physiological basis the two actinomyces are not the same. One is not even a variety of the other, but both are distinct species.

#### CONCLUSION

1. The organism described is a new species. We propose to call it *Actinomyces Moormani* after the technician herein previously mentioned because she was the first to differentiate it from a cornybacterium.

2. It is pathogenic to man, forming chronic abscesses.

3. Like *A. graminis* it is probably found in the mouth as a saprophyte.

4. For the purpose of identification of an actinomyces it is suggested that the media and procedures mentioned herein are all necessary and useful.

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## THE PATHOGENESIS OF HEMORRHAGE IN ARTIFICIALLY INDUCED FEVER\*

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ARTIFICIALLY induced fever has attained a definite place among modern therapeutic procedures. Hyperpyrexia, however, is attended by actual, as well as by potential dangers, as is usually the case with any powerful therapeutic agent. Tissue injury from prolonged or excessive exposure to heat has long been recognized. Two of the most constant pathologic findings under such circumstances have been acute liver damage and hemorrhage. In replies to a questionnaire regarding fever therapy, which was sent to physicians by the Council on Physical Therapy, "several reported instances of cerebral hemorrhage."<sup>1</sup> Five fatalities have been cited by Hartman and Major,<sup>2,3</sup> and Wilbur and Stevens.<sup>4</sup> Necropsy findings included liver necrosis, hemorrhagic pneumonia, hemorrhagic encephalitis involving the vessels at the base of the brain, subconjunctival hemorrhages, submucosal hemorrhages in the trachea, and subendocardial and myocardial hemorrhage.

Pathologic findings in experimental animals subjected to artificial fever by various means have been reported by Baldwin and Nelson,<sup>5</sup> Hall and Wakefield,<sup>6</sup> Hargraves and Doan,<sup>7</sup> Hartman and Major,<sup>2,3</sup> Jacobsen and Hosoi,<sup>8</sup> Mortimer,<sup>9</sup> and von Haam and Frost.<sup>10</sup> Hemorrhages have been reported in each instance. These included hemorrhage into the bone marrow, lymph nodes and splenic pulp, cortex and medulla of the brain, cortex of the adrenal gland, subpericardium and valves of the heart and extravasation of blood into the submucosa and subserosa of the intestines. Liver damage was reported in most instances. Jacobsen and Hosoi found changes in the peripheral zone of the liver lobules and fatty damage to the parenchymatous cells. Hall and Wakefield stated that the initial liver damage was central and "of a milder degree than the necrosis found in acute yellow atrophy." Engorgement of the sinuses, extensive midzone necrosis and hemorrhage into the liver substance were reported by Hartman and Major.

The etiologic mechanism of the hemorrhages invoked by fever has never been entirely satisfactorily explained. Wilbur and Stevens<sup>4</sup> stated that hemorrhage might be due to extreme dilatation of the vessels which allowed extravasation of the red cells, or, possibly, that it was the result of capillary damage not demonstrated anatomically; the liver damage they hypothesized as the direct result of actual heat or as secondary to intoxication. Hartman<sup>2</sup> noted the similarity between the pathologic lesions following fever therapy and those due to prolonged asphyxia in acute alcoholism, carbon monoxide

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or nitrous oxide poisoning. A constant and severe anoxia was demonstrated in experimental animals following induced fever as a result of decreased oxygen saturation of the arterial blood and a low oxygen content of the venous blood. Factors contributing to the anoxia were alkalosis, accelerated blood flow, the increased temperature of the blood and an increased demand for oxygen by the tissues.

Prothrombin, fibrinogen and blood platelets are among the more important known factors essential to the coagulation of blood, and are the products of organs proved to be affected pathologically by high fever temperatures.<sup>11, 12</sup> Prothrombin and fibrinogen are produced in the liver, and platelets arise from the megakaryocytes found principally in the bone marrow.<sup>13</sup> The hemorrhagic diathesis in thrombocytopenic states is well recognized. Hemorrhage may also occur when the prothrombin level falls to below 40 per cent of normal values.<sup>14</sup> Deficiency in prothrombin can be quantitatively determined by the methods of Smith, Warner and Brinkhous,<sup>15, 16</sup> and Quick, Stanley-Brown and Bancroft.<sup>17, 18, 19</sup> These investigators have reported a decrease in prothrombin levels associated with liver damage. More extensive liver necrosis must be present before there is a pathologic decrease in fibrinogen. Smith, Warner and Brinkhous<sup>16</sup> have shown that it is possible to decrease the prothrombin and maintain the fibrinogen level with carefully adjusted amounts of chloroform, a toxic hepatic agent. Larger amounts of chloroform result in a decrease of both factors.

The present study was undertaken to explore further into the underlying mechanism of the hemorrhagic tendency accompanying fever. The icterus index, liver function studies, prothrombin values and fibrinogen determinations were obtained to determine the relative efficiency of the various hepatic functions, and more particularly to detect any significant variation in the products of hepatic origin that are important in the coagulation of blood. Parallel determinations of circulating blood platelets and serial bone marrow biopsies were done. Observations on the number and character of the megakaryocytes were correlated with the level of the platelets in the peripheral blood.

#### METHODS

The method of Quick, Stanley-Brown and Bancroft<sup>17, 18, 19</sup> for prothrombin was used in human patients. This technic proved unsatisfactory for accurate quantitative prothrombin determinations using rabbit plasma. A modification of the method of Quick was devised. Blood from the heart was obtained and mixed with one-tenth its volume of sodium oxalate. The hematocrit and total volume were recorded after centrifugalization. A series of 10 dilutions in saline from 10 per cent to 100 per cent was prepared. Two drops of thromboplastin were added to two drops of each dilution. To this mixture were added four drops of calcium and fibrinogen solution, and the clotting time at 37° C. was recorded. The dilution which clotted in 20 seconds was noted and compared with a known normal plasma. Thus, if a

20 per cent solution of normal plasma clotted in 20 seconds, and a 30 per cent solution of the unknown plasma clotted in 20 seconds, the latter would be 10 per cent less or 90 per cent of normal. By this method rabbit plasma contained about 90 per cent and human plasma about 80 per cent as much prothrombin as dog plasma, which results are comparable to those reported by Smith, Warner and Brinkhous.<sup>14, 15, 16</sup> The method developed by Smith, Warner and Brinkhous is now being used in our laboratory.

The newer method of Greenburg and Mirolubova<sup>20</sup> with the modification suggested by Minot and Keller<sup>21</sup> has been found entirely satisfactory for the quantitation of fibrinogen.

As a further measure of liver function, the standard galactose tolerance and hippuric acid tests have been used in all human case studies. The bromsulphalein test was used giving five milligrams of the dye intravenously for each kilogram of body weight.

In the clinical studies, the sternal puncture aspiration technic was used for obtaining marrow. A different rib interspace was selected for each subsequent observation. Total cell counts were obtained with the standard pipettes and diluting fluids used in peripheral blood studies. The total nucleated cell counts were slightly lower than those reported by Erf.<sup>22</sup> The marrow tissue was studied immediately in supravital stained preparations with differential cell counts, and fixed films were made for Wright's Giemsa staining. The remaining material was allowed to clot, was fixed in Helly's fluid, embedded, and paraffin sections were stained with eosin and hematoxylin.

In rabbits, a preliminary aspiration biopsy of the femur marrow and tissues obtained immediately post mortem were studied by the above methods. Because of the dense cellularity of the rabbits' marrow, accurate total counts were impossible to secure, but differential counts and qualitative changes in the cells were recorded in each instance.

In human subjects the indirect method of Dameshek<sup>23</sup> was used for platelet determinations. Normal counts range between 400,000 and 700,000 per cubic millimeter of blood.

In rabbits a modification of the method of Olef<sup>24</sup> using Dameshek fluid was employed. An area of the ear vein was covered with vaseline and punctured through a drop of fluid preservative. The blood and dye solutions were transferred to a paraffin cup and thoroughly mixed. The film preparations were then made as in the human subjects.

#### OBSERVATIONS UNDER EXPERIMENTAL CONDITIONS

Rabbits were used as experimental animals, fever being induced by radiotherm. No barbiturates or narcotics were used. An individual difference in the susceptibility of the several coagulation factors to fever temperatures was noted in the various animals. During and following artificially induced hyperthermia, there was a decrease in total platelets in all instances, the

lowest determinations being one-fourth to one-third of the pre-fever control values. More or less extensive megakaryocytic damage was apparent during the period of low peripheral platelet values and a prompt and rapid regeneration of new megakaryocytes in the marrow always preceded the return of the circulating platelets to normal levels. A quantitative decrease in prothrombin and fibrinogen occurred in those animals in which liver damage was later found, and where no hepatic damage could be demonstrated, no disturbance in prothrombin had been recorded.

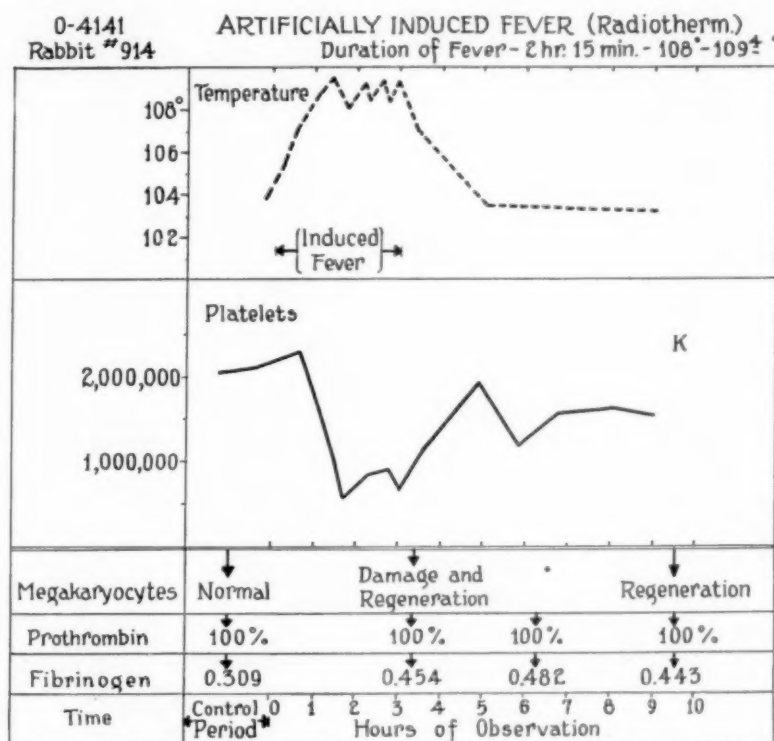
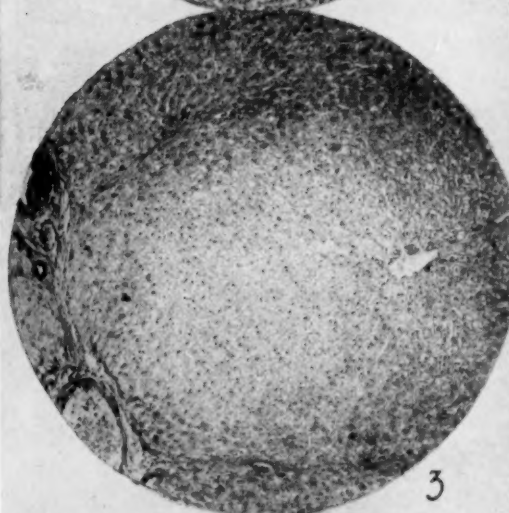


CHART 1.

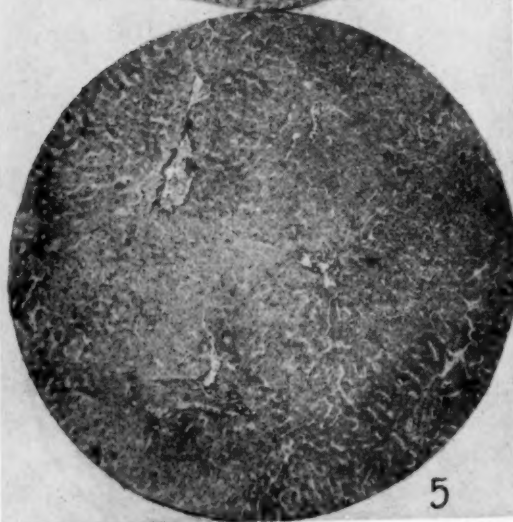
The first rabbit (chart 1) which received two hours and 15 minutes of fever between 108° and 109.4° F., showed a depression in only one of the coagulation factors as a result of hyperpyrexia. During the induction of fever there was an elevation in the platelet level, following which there was a steady decrease to about one-fourth of the control values. The platelets remained at this low level until after the radiotherm induction was discontinued and then gradually rose to slightly below the pre-fever level. There was no quantitative change in either prothrombin or fibrinogen. At necropsy there was no evidence of hemorrhage, either grossly or microscopically. Examination of the bone marrow (plate 1, figure 2) revealed both normal and



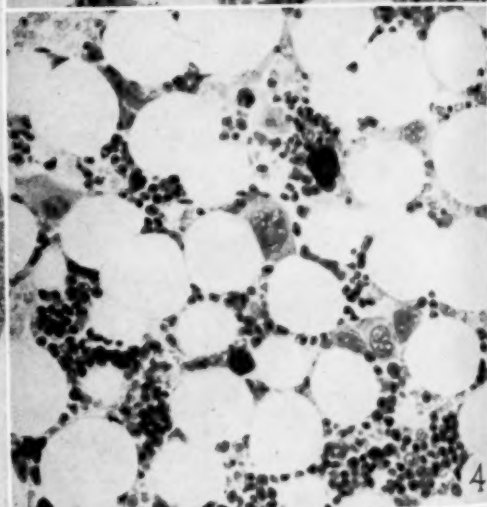
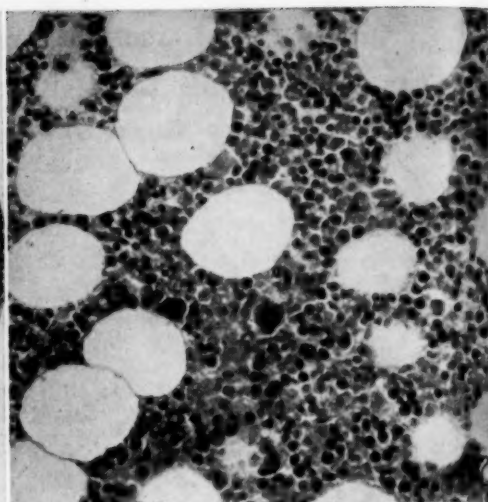
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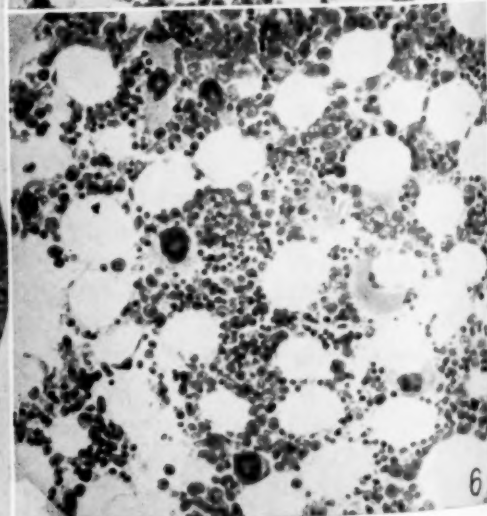
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4



6

PLATE I.

injured megakaryocytes with pyknotic nuclei. There were also young regenerating megakaryocytes. The liver cells were normal (plate 1, figure 1).

A quantitative decrease in platelets, prothrombin and fibrinogen occurred in the second rabbit, febrile for two hours with a gradual increase to

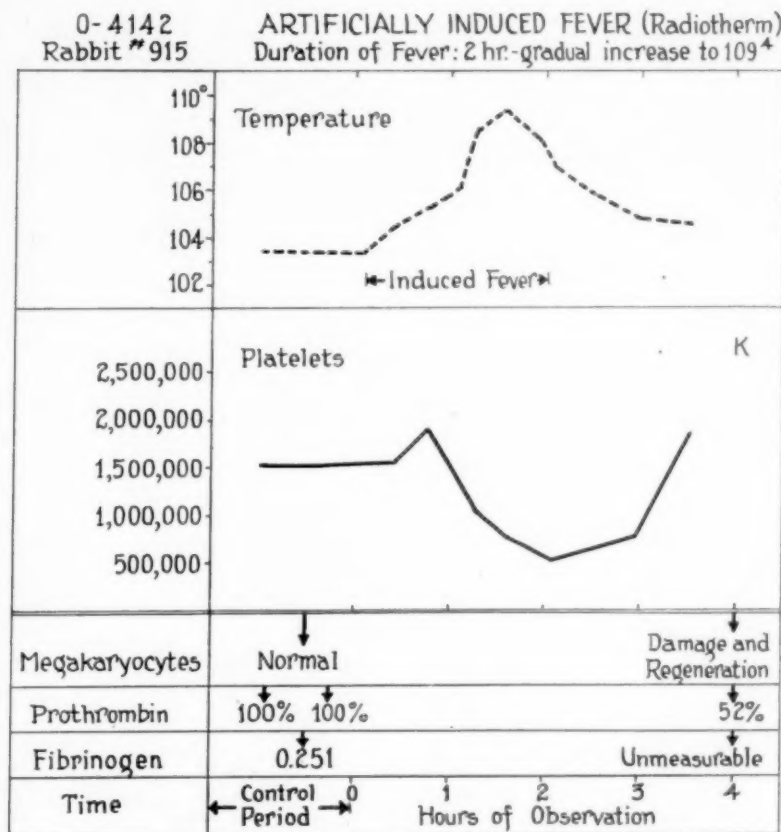


CHART 2.

109.4° F. (chart 2). Early in the period of induction of fever there was again a slight elevation in the platelet level, after which there was a decrease to about one-third of the control level. After the fever was discontinued the platelets returned rapidly to slightly above the pre-fever level. The pro-

PLATE I. Microscopic sections of liver and bone marrow after artificially induced fever.

FIGS. 1 and 2. Rabbit 0-4141. Duration of fever 2½ hours, temperature 108-109.4° F. The liver cells are normal. There are both normal and damaged megakaryocytes with pyknotic nuclei in the bone marrow. See Chart 1.

FIGS. 3 and 4. Rabbit 0-4142. Duration of fever 2 hours, highest temperature 109.4° F. The liver shows some degeneration of the cells in the periphery of the lobule, the cells in the central zone being filled with glycogen. The marrow shows mature normal, damaged, and young regenerating megakaryocytes. See Chart 2.

FIGS. 5 and 6. Rabbit 0-4143. Duration of fever 2 hours, lethal temperature 111° F. Both the liver and the marrow show acute cellular degeneration. The megakaryocytes are distinctly damaged. See Chart 3.

thrombin fell to 52 per cent of normal post-fever. An accurate fibrinogen quantitation could not be made due to the fragility of the fibrin clot. The bone marrow was examined after the animal was sacrificed, and there were normal, mature, damaged, and young regenerating megakaryocytes found side by side (plate 1, figure 4). The liver showed degeneration of the cells in the periphery of the lobule, the cells in the central zone being filled with glycogen (plate 1, figure 3). Small punctate hemorrhages were seen grossly

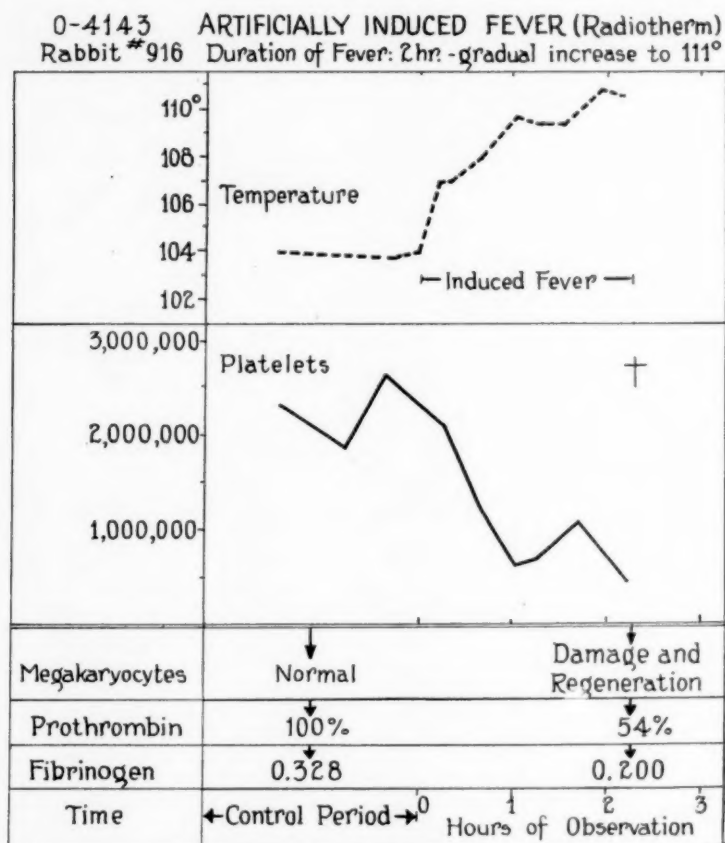


CHART 3.

in the lymph nodes, thymus and bone marrow. Microscopic examination revealed an early hemorrhagic pneumonia.

Fever induction was lethal after a gradual increase to 111.0° F. in two hours in the third rabbit (chart 3). There was a continuous fall in the platelet level, and the prothrombin immediately before the death of the animal had decreased to 54 per cent of normal. There was a similar decrease in the fibrinogen. Examination of the bone marrow revealed nuclear damage to the majority of the mature megakaryocytes, although a beginning regeneration of very young cells could be seen (plate 1, figure 6). Micro-

scopic examination of the liver revealed acute cellular degeneration (plate 1, figure 5). There was gross hemorrhage into the substance of the lymph nodes. Small punctate hemorrhages were grossly visible in the thymus. Microscopic examination revealed an early hemorrhagic pneumonia and small focal hemorrhages and swollen hemorrhagic glomeruli in the kidney.

## OBSERVATIONS IN HUMAN DISEASE

The patients selected for this study were all young adult individuals, normal to complete physical and laboratory examinations except for some type of gonorrheal infection. The galactose tolerance, hippuric acid and brom-

0-4036 C.H. q  
Aged 20 years

FEVER THERAPY - 1st. Treatment  
Duration of Fever:  $106^{\circ}$ - $107^{\circ}$ =9 hr.;  $104^{\circ}$ - $107^{\circ}$ =10 hr. 30 min.  
G.C. Arthritis

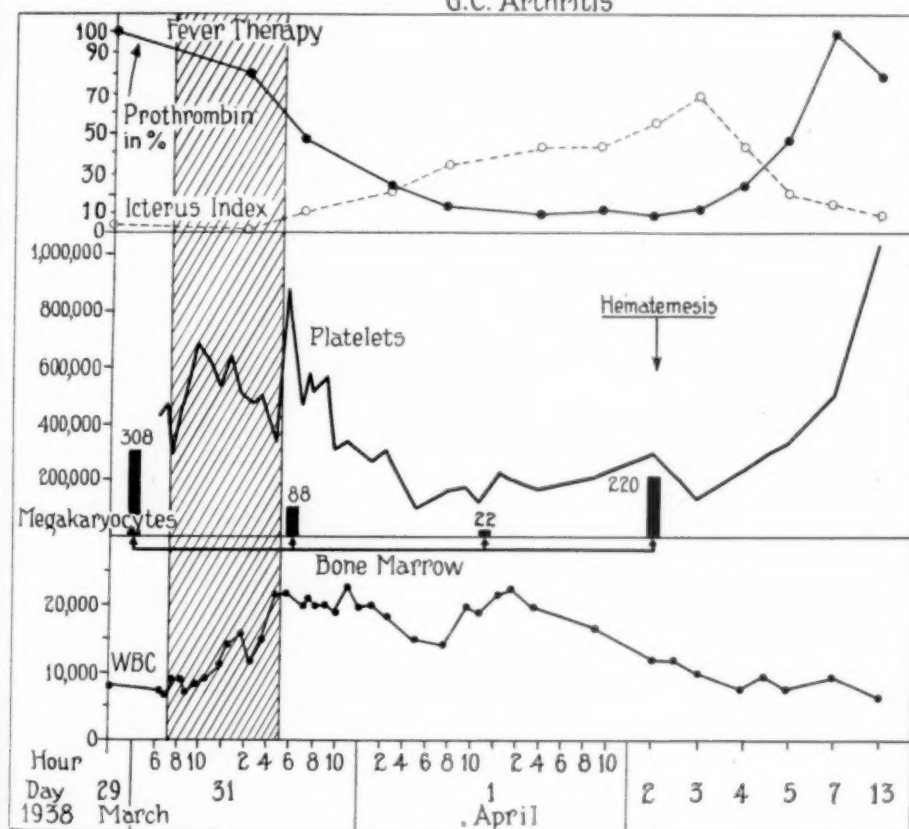


CHART 4.

sulphalein dye tests were normal before therapy in each individual. Only the bromsulphalein dye test could be repeated satisfactorily post-fever because of nausea and vomiting. Artificial fever was induced by the Kettering hypertherm. As in the experimental animals there was an individual va-

riation from patient to patient in the susceptibility of the several coagulation factors to fever temperatures. The observations in the human subjects differed further in that the major decrease in the coagulation elements occurred only some time after the defervescence of fever and the compensatory regeneration and recovery became apparent after a considerably longer latent period than was reported in the experimental animals.

A marked decrease in prothrombin followed 10 hours of therapy in the first patient (chart 4). This is the only patient who was not given large

0-3987. C.B. ♂  
Aged 28 years.

FEVER THERAPY—3rd. Treatment.  
Duration of Fever:  $106^{\circ}$ – $107^{\circ}$ =6 hours.  
G.C. Arthritis

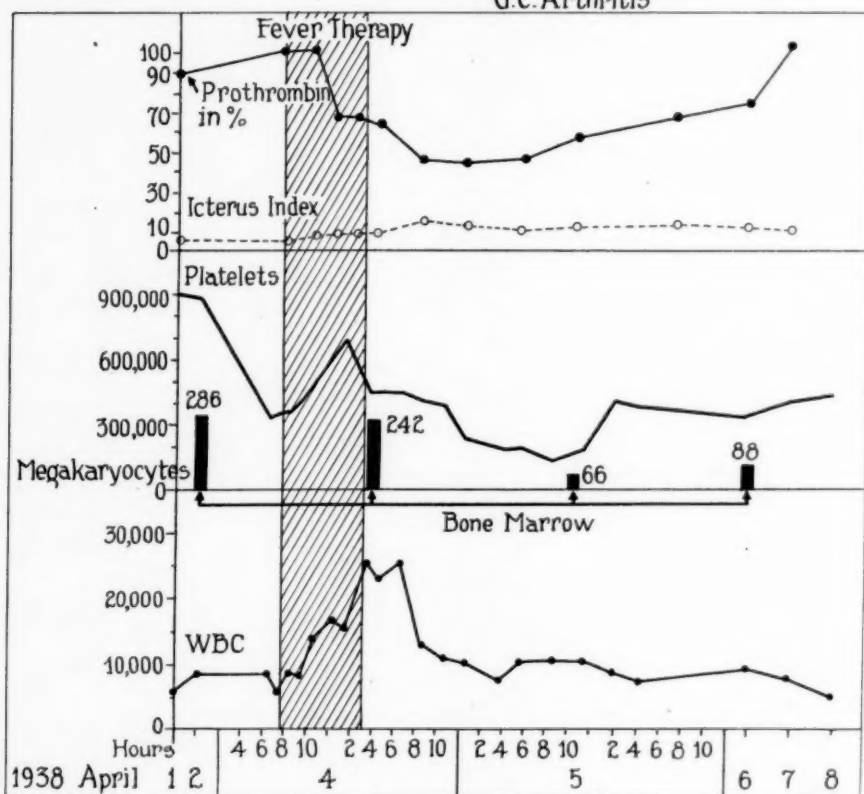


CHART 5.

amounts of glucose preparatory to hyperthermia. During the actual treatment there was a slight elevation in the blood platelets and only a slight decrease in the prothrombin. Immediately after hyperpyrexia there was a retention of bromsulphalein, 15 per cent in one-half hour and 5 per cent in one hour. There had been no retention previous to treatment. The galactose tolerance and hippuric acid tests could not be repeated because of nausea and vomiting. Sternal puncture at this time revealed, in addition to dam-

aged megakaryocytes, an increase in the phagocytic clasmatocytes and a decrease in the more mature neutrophilic myelocytes as contrasted with the pre-fever marrow study. Subsequently there was a progressive decrease in prothrombin and blood platelets and a gradual increase in the icterus index to 70 units, 72 hours post-fever. Hematemesis occurred on the second post-fever day, at which time the prothrombin reached its lowest point of 11 per

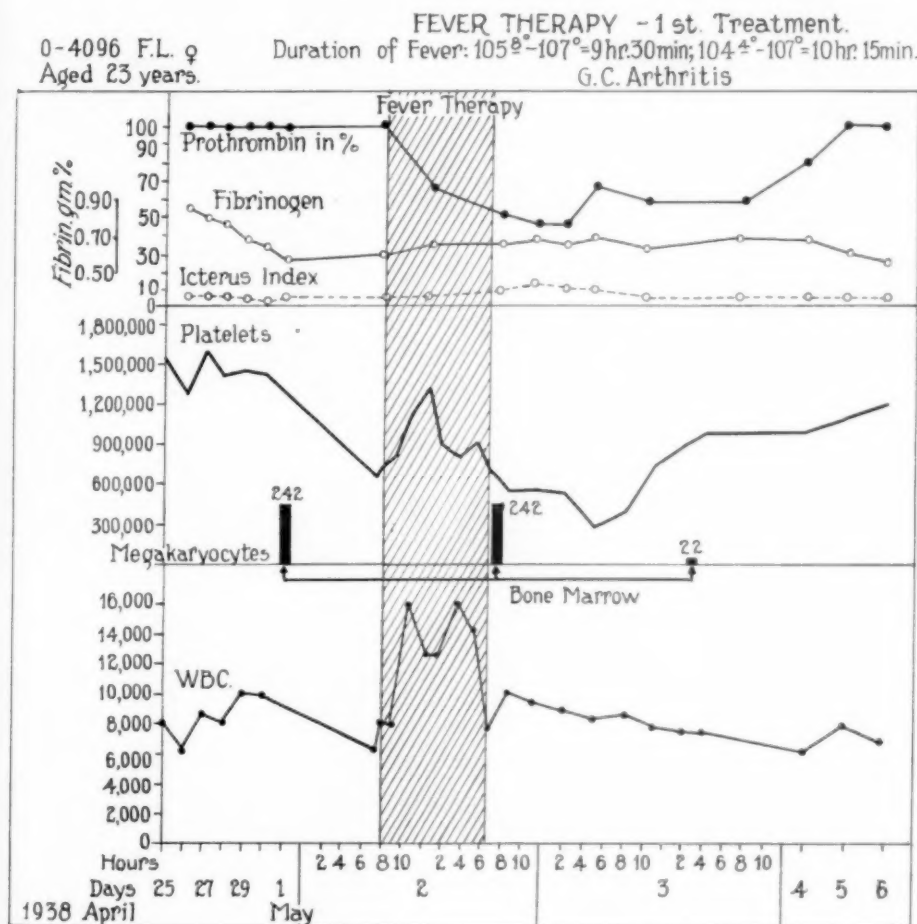


CHART 6.

cent of normal and the platelets were only 200,000 per cu. mm. Both of these coagulation factors had returned to normal by the seventh post-fever day. In the second patient, fortified by glucose during the 48 hours pre-fever, the decrease in prothrombin and in blood platelets did not progress to the point of hemorrhage (chart 5). Again the major deflections occurred only after the body temperature had returned to normal. Immediately post-fever there was a retention of 20 per cent bromsulphalein in 30 minutes

0-2065 E.M.R. ♀ Post Splenectomy (3yr. 10mo) for Purpura Hemorrhagica: G.C. PELVIS, Acute.  
Aged 21 years.

**Fever Therapy**

Duration of Fever: 106° - 107° = 10 hr.

104° - 107° = 11 hr. 15 min.

**Fever Therapy**

Duration of Fever:

105° - 106° = 5 hr. 15 min.

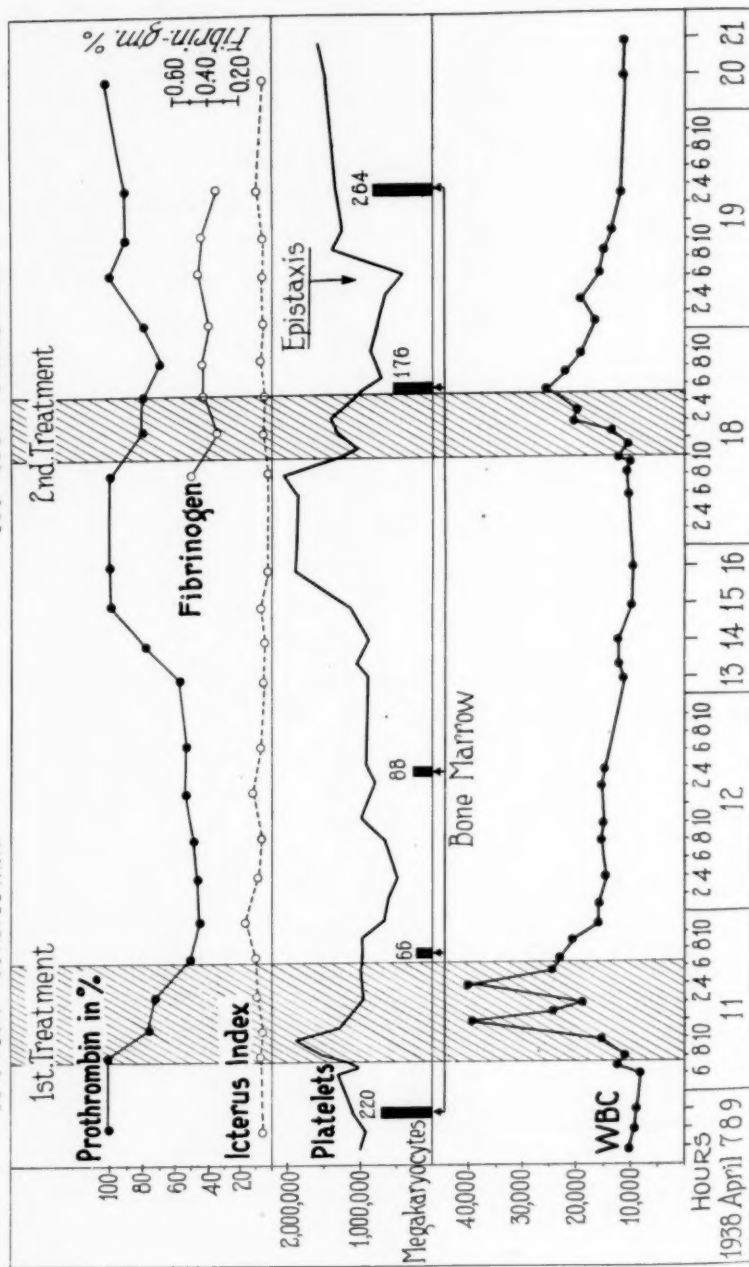


CHART 7.

and 10 per cent in one hour. The highest elevation reached by the icterus index was 13.9 units, five hours post-fever. In addition to damaged megakaryocytes in the bone marrow, there was a moderate "left shift" in the neutrophilic myelocytes and an increase in the highly phagocytic clasmatoctes. Normal equilibrium had been reestablished by the seventh post-fever day.

Observations on the third patient (chart 6) included the effect of hyperpyrexia on fibrinogen. During the period of control observations previous to the fever treatment, a decrease in the blood platelets and fibrinogen was recorded coincident with the gradual subsidence of the more acute arthritic symptoms in the patient. The therapeutic fever had no further effect on the

#### ETIOLOGY OF HEMORRHAGE IN ARTIFICIALLY INDUCED FEVER

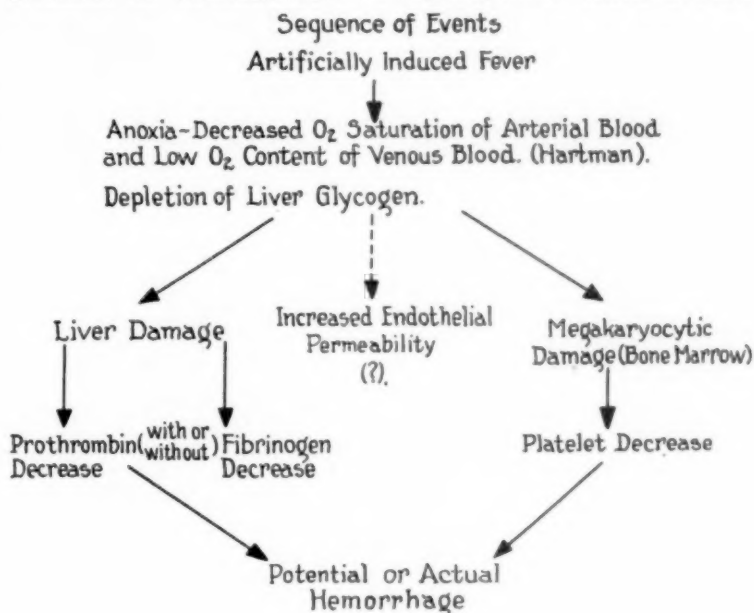


CHART 8.

amount of fibrinogen in the blood plasma. Some deleterious influence on liver and bone marrow, however, was reflected by a moderate decrease in prothrombin and blood platelets as in previous patients, but not to the same degree. A liver function test immediately post-fever showed 15 per cent retention of the bromsulphalein dye in 30 minutes and 10 per cent in one hour. The bone marrow revealed definite nuclear megakaryocytic damage, but no decrease in neutrophilic elements and no increase in phagocytic clasmatoctes. There was a complete return to normal of all factors by the fifth post-fever day.

An especially interesting study of the effect of hyperpyrexia on the several coagulation factors was made in a former patient from our hematologic

clinic who had had a splenectomy three years and 10 months before for thrombocytopenic purpura (chart 7). No bleeding of any kind had occurred in the interim and two normal pregnancies had been uneventfully consummated. Two fever treatments, the first of 10 hours, the second of five hours duration, were given for an acute gonococcal pelvic inflammatory infection. After each treatment there was a temporary decrease in prothrombin and blood platelets. Epistaxis occurred after the second treatment with moderately depressed prothrombin and with the platelets at their lowest level, 404,520 per cu. mm., the majority being extremely small and qualitatively altered units. There was no recorded change in the fibrinogen. Whereas there had been no retention of bromsulphalein before hyperpyrexia, after the first treatment there was 14 per cent retention in 30 minutes and 12 per cent in one hour, and after the second treatment there was 10 per cent retention in 30 minutes and 8 per cent in one hour. The bone marrow revealed moderate megakaryocytic damage and an increase in the phagocytic clasmatocytes after each treatment. There was a rapid return of all elements to normal after each treatment.

#### DISCUSSION

Hartman<sup>3</sup> has shown that hyperpyrexia may lead to anoxia. It is a well established fact that prolonged anoxia will result in damage to the hepatic cells. Liver damage has been found to accompany the anoxia which occurs during anesthesia.<sup>25</sup> Hepatic cell injury is more readily accomplished with chloroform in an undernourished animal than in the well fed animal whose hepatic cells are full of glycogen. Acute parenchymatous degeneration of the liver cells has been described in all the human subjects examined post mortem following death attributable to therapeutic fever.

Microscopic examination of the liver in the experimental animals in this series revealed acute liver degeneration, the damage being mild in degree in some animals, more marked in others, the quantitative blood prothrombin and fibrinogen determinations being directly proportional to the extent of the tissue destruction.

The state of the liver in human subjects could only be studied indirectly by means of the various tests for liver function. A pathologic retention of bromsulphalein occurred in each instance and was accompanied by a more or less marked increase in the icterus index. A decrease in prothrombin was observed in each patient studied, being more marked in some than in others. The fibrinogen was apparently not affected under the conditions existing in these studies, which finding is in accord with the results reported recently by Ham and Curtis.<sup>26</sup> Prothrombin is thus affected more sensitively than fibrinogen, probably on the basis of the relative degree of liver damage necessary to interfere with these respective functions as described by Smith, Warner and Brinkhous.<sup>16</sup> It is significant that the most marked disturbance in hepatic function occurred in the patient who was not given extra glucose during the immediate prefever period.

Hyperpyrexia under the conditions of these observations, invariably resulted in a decrease in the blood platelets, both in the experimental animals and in the human subjects, recovery taking place more promptly in the former than in the latter. In human subjects the fall in the platelet level occurred in the post-fever period, following a transitory increase during the actual fever episode. Following the thrombocytopenia there was a slow return of the platelets to the circulation. The changing level of the platelets in the peripheral blood reflected directly the state of the megakaryocytes in the bone marrow. There was definite cytoplasmic and nuclear damage during the thrombocytopenic period. The resumption of a normal platelet level was accomplished only after megakaryocytic regeneration was complete in the bone marrow. The decrease in platelets was not mediated through any splenic factor as the same changes occurred in one of our patients who had had a splenectomy for thrombocytopenic purpura approximately four years previous to hyperpyrexia.

The sequence of events in the pathogenesis of hemorrhage in artificially induced fever may then be reconstructed as follows: the rise in temperature causes anoxia and a depletion of the liver glycogen, which in turn result in hepatic damage. With sufficient liver damage (more likely to occur during glycogen deficit) there is a decrease in prothrombin with or without a decrease in fibrinogen. The injury to megakaryocytes is reflected by a decrease in the circulating blood platelets. Damage to the endothelial cells has not been demonstrated morphologically.\* The decrease in platelets, prothrombin and fibrinogen individually and collectively, contribute to potential or actual hemorrhage.

#### CONCLUSIONS

The effect of artificially induced fever on factors important in the coagulation of blood has been studied in experimental animals and in selected human subjects.

A decrease in prothrombin and fibrinogen occurred secondary to liver damage. A decrease in prothrombin may occur without a decrease in fibrinogen.

Artificially induced fever resulted in a relative and absolute thrombocytopenia. The megakaryocytes in the bone marrow showed definite cytoplasmic and nuclear damage. The degree of thrombocytopenia depended upon the extent of the megakaryocytic damage.

The pathogenesis of hemorrhage in artificially induced fever may be followed in orderly sequence: the elevation of body temperature results in anoxia and a depletion of liver glycogen; these factors may result in hepatic and megakaryocytic damage following which there is a decrease in prothrombin and circulating platelets. Fibrinogen may also be decreased. Any

\* Since this manuscript was submitted for publication, Rossman<sup>27</sup> has reported low levels of capillary resistance, measured by a negative pressure suction test, during artificially induced fever.

decrease in these factors important in the coagulation of blood, contributes to potential or actual hemorrhage.

The regeneration of the damaged parenchymatous tissues apparently takes place quite promptly and completely, the changes being reversible within the usual limits of therapeutic application. Any lack of appreciation of the full significance, however, of the facts of mineral, carbohydrate, oxygen, vitamin and water metabolism in fever therapy might lead to irreversible changes and serious permanent damage or death.

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## PARASITOLOGY; A ROUND TABLE DISCUSSION \*

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THE subject of Parasitology is entirely too comprehensive to be treated as a whole in this round table discussion, because it may be interpreted as including not only the field of Animal Parasitology, but also that of Bacteriology, of Mycology, of the viral diseases and of spirochetal infections. Since all of the questions which were submitted to me, with one exception, are in the field of Animal Parasitology, and since I am competent to consider only that subject, discussion will be limited to this field.

Even Animal Parasitology is an extremely large subject, in which a tremendous amount of progress has been made during the past decade, particularly on the clinical and epidemiological sides. I realize that a physician—a practicing physician who is busy with his patients—cannot be a master of all phases of Animal Parasitology. However, it is important for him to know (1) the recognizable characters of the organisms which parasitize man; (2) the most efficient methods of diagnosis; (3) the sites where the parasites reside in the human body; (4) whether or not the parasites are always pathogenic or are potentially pathogenic; (5) if pathogenic, what local and systemic changes they produce in the body; (6) what cardinal symptoms they evoke; (7) what therapeutics is most efficient well within the tolerance of the patient, and (8) how to prevent infection or reinfection.

As residents in North America, we are interested primarily in those animal parasites which reside in our own area, and especially those which are either prevalent or are clinically important. I make this distinction because some parasites of man, which are relatively common, are non-pathogenic, while others are of considerable clinical significance. In North America, the following forms fall into one or the other of the two categories mentioned:

(a) *Intestinal Protozoa*. The intestinal forms include the intestinal amebae (of which there are *Endamoeba histolytica*, the pathogenic form, and five non-pathogenic species), and the intestinal flagellates, as *Trichomonas*, *Chilomastix* and *Giardia*.

(b) *Intestinal Helminths*. There are several relatively common species of intestinal helminths, including *Ascaris*, the seatworm or pinworm (*Enterobius vermicularis*), the American hookworm (*Necator americanus*), *Strongyloides*, the whipworm (*Trichocephalus trichiurus*), the beef tapeworm (*Taenia saginata*) and the dwarf tapeworm (*Hymenolepis nana*).

This list is not exhaustive but contains the more prevalent of the intestinal parasites in our area. Of the intestinal Protozoa and most of the roundworms and the dwarf tapeworm, we find a higher incidence in the

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South than in any other parts of the country, while the beef tapeworm is well distributed throughout the continent of North America.

In addition to these intestinal forms, we have the so-called "trichina" worm (*Trichinella spiralis*). This is relatively common as a clinically important parasite in the East, North and West of the Continent, but is rarely of clinical significance in the South.

Aside from these forms, we have one other group of protozoan parasites, the malaria plasmodia, which are of distinct clinical and public health importance in the warmer zones of North America, not only in the Gulf Coast and South Atlantic States, but extending as far north as the Great Lakes and even into the Far West, in the Columbia River Valley and in the Imperial and San Joaquin valleys in California.

I have attempted more or less to unify this Round Table discussion, based on the questions which were presented. The three important topics that have been requested are: (1) amebiasis, and the intestinal flagellate infections; (2) the intestinal helminthiasis, and (3) the rôle of animal parasites in pulmonary disease. We shall take them up *ad seriatim*. After a consideration of each of these topics, the round table will be opened for general discussion.

#### AMEBIASIS

*Etiology and Geographical Distribution.* Amebiasis is the clinical entity which is produced by *Endamoeba histolytica*, the ameba which invades the tissues of the human body. It is distributed quite generally over the Globe, from the Tropics to the outer limits of the Temperate Zones. It is more common in the Tropics than along the Gulf Coast States. It is more common here in the South than it is in the northern part of the United States, but surveys that have been made in Tennessee, in New York City, Philadelphia, Chicago, Rochester (Minnesota), San Francisco, Los Angeles, Montreal, Saskatoon (Saskatchewan), and in many other localities indicate that this ameba is quite widely distributed throughout the Continent of North America.

*Pathogenicity.* There is essential agreement that *E. histolytica* is either actually pathogenic or is potentially pathogenic. There is no conclusive evidence that it is ever intrinsically non-pathogenic or lacks the potentialities of pathogenicity.

*Types of Amebiasis.* Based on various conditioning factors, we have different pathological and clinical types of amebiasis. Some of these factors are as follows:

(1) *The Levels of the Bowel Which Are Invaded.* In general, *E. histolytica* invades or has the possibilities of invading any site in the large bowel and the last few inches of the ileum, but the two areas in which the preponderance of lesions occurs are the region of the cecum, appendix, and adjacent colon (*cecal amebiasis*), and the rectum and sigmoid (*rectal amebiasis*). Those areas, more than any others in the bowel, are pathologically and

symptomatically significant, and this fact must be taken into consideration in evaluating the problem of amebiasis.

(2) *The Depth of Invasion of the Bowel Wall.* In some instances, there is very shallow invasion, only the superficial portion of the mucosa being invaded and necrosed. In other cases, perhaps in the majority, some of the amebae get down into the submucosa and muscular coats, to form pockets and to spread out by radial extension and coalescence. The lesions in uncomplicated amebiasis are, of course, superficially discrete and distinct from one another. They may be few in number or they may be "peppered" into the mucosa of the large bowel. While they may be confluent below the mucosa, examination of the surface usually will reveal only discrete lesions, in contrast to bacillary infection, in which extensive superficial areas are involved.

(3) *Primary and Secondary Foci.* Both experimental and postmortem evidence favors the view that a majority of the primary sites, where the amebae become attached to the intestinal wall, or obtain a foothold, are in the region of the cecum and the appendix, although in some patients colonization may first occur lower in the bowel. Secondary foci may develop from the extrusion, from the primary lesions, of amebic progeny, which become implanted in other sites lower in the bowel. Likewise, when amebae get down deep enough to invade the mesenteric venules, they are carried to the liver, the organ in which the highest incidence of amebiasis occurs outside the bowel. In the liver, there may be small multiple foci or one or more large abscesses. By extension through the diaphragm, the amebic process may reach the pleural cavity and the lungs. However, there is the possibility that amebae may get out of the bowel wall through the mesenteric lymphatics and become implanted in the lungs, without ever having passed through the liver; or they may pass through the pulmonary capillaries and become implanted in foci beyond the lungs. Thus, there are cases of amebiasis of the brain, spleen, urinary tract, the lymphatics and the skin, and one authentic report each of amebiasis of the epididymis and the scrotum. Most frequently, cutaneous amebiasis is a direct perianal extension from foci just within the rectum.

*Symptomatology.* The next phase of the subject embraces the symptoms that are evoked by the presence of *Endamoeba histolytica* in the body. They are usually classed as acute, subacute, chronic or carrier types. The older classification is based primarily on our previous conception of symptoms, namely, dysentery or profuse diarrhea produced by amebic lesions in the lower portion of the colon and the rectum. However, this conception is quite unsatisfactory, since we now realize that the most common focus of infection is at the level of the cecum, appendix and ascending colon. This cecal type of amebiasis is frequently unaccompanied by dysentery, or the signs or symptoms that are so closely associated with the rectal or sigmoid type. In the cecal type, there may be evidence of a subacute or a chronic appendicitis, or a suggestion of gall bladder disease, or of peptic ulcer; or

there may be only a general malaise. We are now reorganizing our clinical classification of amebiasis, based on the new conceptions. Furthermore, many so-called "carriers" actually have symptoms, provided care is taken in discovering the symptoms. Yet there are many carriers, perhaps the majority, who have no objective or subjective evidence of tissue invasion, although there is always the likelihood that they will develop a clinical amebiasis whenever their threshold of resistance is sufficiently lowered.

*Diagnosis.* Diagnosis may be based on subjective and objective symptoms, on the gross character of the stool; whether, in the dysenteric type, there is an excess of red blood cells or white blood cells, and on the type of tissue exudate. However, only microscopic examination of the stools provides specific evidence of infection. When we examine stools for amebae, we grossly classify them as liquid (i.e. diarrheic, dysenteric, and the like), semi-formed or formed. In the unformed stool, it is not common to find any stage of *E. histolytica* except the trophozoites, the motile stage of the parasite. On the other hand, in the formed stool, we find no trophozoites, only the encysted stage, or occasionally the precyst. The unformed stool should be examined while fresh. By fresh, we mean that it should not be allowed to cool, that it should be examined within half an hour after it is passed. Although, at times, trophozoites survive a longer period, this chance should not be taken. Well-formed stools may be kept 24 hours in a cool place without endangering diagnosis.

In addition to fecal examination, we have examination of proctoscopic material. If amebae are actually found by proctoscopic technic, there is no question about the diagnosis, but a negative proctoscopic examination does not necessarily mean a negative diagnosis, because the major portion of the bowel cannot be examined by the proctoscope. Then, there is roentgen-ray examination, which is more likely to provide suggestive evidence for lesions in the upper half of the large bowel than for the lower half. At times, the roentgen-ray film shows "moth-eaten" or other types of defects which might be due to amebic ulceration, but the roentgen-ray should never be used to take the place of microscopic examination for the diagnosis of amebiasis.

I know of no new or better way of making diagnosis than recovering the organisms by means of microscopic examination of the patients' feces or by examination of material obtained through the proctoscope or following a saline purgation or enema. Let me reemphasize the necessity for having fresh material; if it is liquid, after standing for hours, it is usually undiagnosable, or, at best, it places the diagnostician in an embarrassing position. For trophozoites, we, in our laboratory, as those in many other laboratories, examine coverglass mounts of the direct fecal film, unstained and iodine-stained, by making two side-by-side preparations, one an unstained fecal film made up in one or two drops of physiological salt solution, and the other, after adding and mixing one drop of D'Antoni's iodine stain to the fecal material. For cysts, however, we have now perfected the zinc sulphate cen-

trifugal floatation technic. This technic concentrates cysts many-fold compared with the unconcentrated film, and has the advantage over brine floatation in that the cysts are essentially unshrunk. They are not only in a diagnosable condition but also in a viable state, so that if you wish to plant them for culture growth, they are available for that technic. In some laboratories the hematoxylin-stained preparations are used. They have the disadvantage of requiring several hours to prepare. On the other hand, they have the advantage of providing a more or less permanent film, which can be studied and diagnosed at leisure. Some laboratories prefer them to the iodine-stained film; some prefer the iodine-stained film; some use both.

*The Incidence of Clinical Amebiasis.* Clinical amebiasis is found primarily between 20 and 50 years of age, with the peak between 30 and 40. It is more common in whites than in negroes; more common in males than in females. I do not know about its relationship to the economic status, because most of our private patients who have clinical amebiasis come from the upper economic strata, while most of those in the Clinic come from the lower economic strata. It may be said with certainty that all economic groups of the population are susceptible to infection, but not necessarily equally exposed. There are various predisposing factors to infection, including differences in pathogenicity of the strains of *E. histolytica*, although all North American strains thus far tested have proved to be pathogenic; different predisposing factors within the patient himself at the time he is exposed to infection, as malnutrition (with its invariable lowering of the threshold of resistance), excess of carbohydrates and an insufficiency of proteins, dietary and alcoholic indiscretions, physical and mental strain, worry, loss of sleep, as well as intercurrent infections lowering resistance.

It is impossible to leave this phase of the subject without considering *amebic liver abscess*. This variety of amebiasis was first studied clinically by Sir Leonard Rogers in Calcutta, Musgrave in Manila, Deeks and James in the Canal Zone. The most recent contribution is that of Ochsner and his associates in New Orleans. One of the questions proposed for this discussion was, "How about the correlation of amebiasis with pulmonary tuberculosis?" There is very little information on the subject. In Ludlow's series in Korea (1926) with 150 cases of amebic liver abscess, 10 per cent of those entered the pleural cavity by rupture or extension; only two of the cases had concurrent tuberculosis. In a report of pulmonary amebiasis by Keeton and Hood (1938), tuberculosis was found to be secondary in one of their five cases. These workers indicated, however, that it was frequently difficult to make a clinical diagnosis which would rule out tuberculosis on the one hand and pleural amebiasis on the other, without careful laboratory examinations.

*Treatment.* With reference to the treatment of amebiasis, I shall enumerate the more important drugs, taking them up from the historical point of view. They are as follows:

1. *Ipecac*. This drug was first used in 1829 and popularized many years later by Sir Leonard Rogers in Calcutta, towards the beginning of the present century. Dover's powders and alcestra tablets were later introduced. Although ipecac has been a standard prescription for amebiasis until recently, any physician planning to prescribe this drug should first take a full course of ipecac himself.
2. *Emetin hydrochloride*. This was first proved valuable by Vedder in 1912, and still has its place, but it should not be abused. It is very valuable in reducing acute manifestations but is probably not curative. It should not be prescribed in excess of one grain daily for a total of 12 grains. When given in larger amounts, it has serious sequelae, including degenerative myocarditis.
3. *Bismuth subnitrate*. Deeks, in 1908, introduced this drug in the Ancon Hospital, in the Canal Zone. I know of no specific amebicidal property in this drug. However, it may alleviate the more acute symptoms of amebic dysentery until the patient can obtain specific treatment. It has the special disadvantage of masking the amebae so that they cannot be readily diagnosed microscopically.
4. *Stovarsol* (190 Forneau). This French preparation had its place in its day and still has its advocates. While it constitutes rather a heroic treatment, it has cured many persons who have been able to take a full course of treatment.
5. *Chiniofon* (yatren, anayodin). This drug was first introduced by Mühlens in 1921, and has come to be used as probably the most common drug for the treatment of all types of amebiasis. It has a very high amebicidal rating and a very low toxicity.
6. *Vioform*. Second to chiniofon, in the same chemical series, but containing more iodine, is vioform, which was introduced by workers in California (David, Johnstone, Reed and Leake, 1933). Both chiniofon and vioform are usually prescribed in the amount of three or four 4-grain tablets, three times daily, for a period of eight to ten days.
7. *Diodoquin*. This drug is relatively inefficient, because it is not readily absorbed by the bowel wall, and hence does not reach the organisms in the deeper layers of the bowel.
8. *Carbarsone*. About the same time that vioform was introduced clinically, carbarsone was introduced by Anderson and Reed (1931) in California. The dose prescribed is usually two 4-grain tablets daily for eight to ten days.

In passing, I wish to state that at times one of the usual amebicidal drugs may not completely eliminate the infection. In that case, one of the other available drugs should be utilized.

## INTESTINAL FLAGELLATE INFECTIONS

In referring to the intestinal flagellates, mention may be made, in passing, of *Trichomonas* and *Chilomastix*, which live in the lumen of the cecum and, in so far as we know, are not tissue invaders. *Giardia* lives primarily in the region of the duodenum. It also is not a tissue invader; however, it has a ventral adhesive disc, by which it can attach itself to the cuticula of the mucosa, so that, in tremendous swarms, as exist in many *Giardia*-infected patients, it is possible for *Giardia* to produce a superficial erosion of the mucosa, with an excess of mucus, and a mucous diarrhea. Since 1937 atabrine, administered as in malaria, has been utilized in the treatment of 417 cases of giardiasis, with eminently successful results. Chiniofon is at times helpful; carbarsone may be helpful. At times neither of these drugs produces more than a temporary diminution in the mucous diarrhea or in the number of organisms in the bowel. Glauber salts may be given as a temporary palliative.

Before I pass on, are there any questions on amebiasis or flagellate infections of the intestinal tract?

Question: What percentage of zinc sulphate is used in the zinc sulphate centrifugal floatation technic?

Answer: It is made up as a 33 per cent aqueous solution of zinc sulphate U.S.P., having the specific gravity 1.180.

Question: What about the technic for diagnosis of amebae in the tissues at post-mortem?

Answer: If a "fresh" autopsy has been secured, routine hematoxylin-eosin preparations are satisfactory. For older sections, the addition of Best's carmine to the hematoxylin-eosin technic stains the amebae a strawberry red, so that they can be readily found and identified.

Question: Do you consider carbarsone valuable?

Answer: Yes, but hardly as satisfactory as chiniofon and somewhat more toxic.

Question: Has diodoquin been proved to be satisfactory for amebiasis?

Answer: Cases treated with this drug are more likely to relapse, because the drug is not readily absorbed by the deeper layers of the bowel and thus kills only those amebae near the surface.

Question: What is your opinion about serologic tests for amebiasis?

Answer: Complement-fixation has proved to be at least 90 per cent specific in diagnosis. I think it is particularly valuable as a post-treatment check in patients whose feces are repeatedly negative.

Question: Is there any correlated blood change in amebiasis?

Answer: In uncomplicated amebiasis there is no blood change.

Question: Do you use the iodine in the tincture form for staining amebae?

Answer: We use D'Antoni's iodine solution. The stock is made up as a saturated solution of iodine in a 1 per cent aqueous solution of potassium iodide.

Question: Have you used quinine for the treatment of giardiasis?

Answer: I have had no experience myself.

Question: It was used in one case in Philadelphia.

## INTESTINAL HELMINTHIASES

The next phase of the subject deals with intestinal helminthiases. I shall confine consideration exclusively to treatment. I might mention, however, that ascariasis and dwarf tapeworm infection are found more frequently in younger children, while the other helminthic infections are more prevalent in older children and adults. Diagnosis is made by recovery of worms or their segments, their eggs or larvae.

We have some anthelmintics which have been handed down to us from the ancients, as infusion of the bark of *Punica granatum*, *semen contra*, and decoction of male fern; others from American aborigenes, as oil of chenopodium and leche de higuerón. From the Greeks came the unrefined plant products from which we have obtained thymol, santonin, oil of chenopodium (with its effective fraction, *ascaridol*), the oleoresin of male fern, and from the Egyptians, pomegranate bark from which we have extracted pelletierin tannate or pelletierin hydrochloride. Those drugs which were pharmaceutically and biologically tested before they were used clinically include carbon tetrachloride, tetrachlorethylene, hexylresorcinol and gentian violet. From these groups, I shall mention certain drugs which are particularly recommended for their combined efficiency and safety.

1. *Ascariasis*. The drug of choice is hexylresorcinol, in the form of caprokol pills, with hard gelatin coating, on the market in 0.2 gm. size and soon available also in 0.1 gm. size for small children. The dose for adults is 1 gm., taken in the morning on an empty stomach, and followed by a four to five hour fast. In ascariasis, I advise post-treatment saline purgation to secure rapid evacuation of dying worms, which might otherwise produce acute intoxication of the patient, due to absorption of their products of decomposition.

2. *Oxyuriasis*, or pinworm infection. Prescription of caprokol pills, as indicated above in ascariasis, followed the same night by retention enemas of hexylresorcinol 1:1000 solution (S. T. 37 undiluted) after the large bowel has been cleaned out with high tepid water enemas, has proved fairly effective. As an alternative, gentian violet therapy, given in the form of seal-ins-coated tablets (one grain three times daily for a period of a week or eight days, then rest a week, then a second period of a week or eight days' treatment) may be employed, and has been found to have a 90 per cent efficiency. However, pinworms in a family or institutional groups will not be eliminated unless all infected members of the group are treated until they are cured.

3. *Hookworm infection*. Both tetrachlorethylene and carbon tetrachloride are very efficient. Tetrachlorethylene is preferable because it is almost insoluble in water and, therefore, in the absence of alcohol or absorbable oils, is essentially non-toxic, since it is not absorbed by the bowel wall. In utilizing either drug, both pre-treatment and post-treatment purgation with Glauber salts is recommended, not only to clean out the bowel but

to remove the mucus from around the heads of the worms, thus allowing the drug to act more rapidly through the mouth of the worm.

4. *Trichocephaliasis* or whipworm infection. There is no safe, specific drug available in the United States. In Tropical America, the leche de higuerón, or juice of *Ficus glabrata*, either fresh or preserved in 1 to 2 per cent sodium benzoate, is administered in two-ounce amounts. As "Higueronia," it may be obtained from Mexico City or Cali, Colombia, but it is not available in the United States as far as I know. This crude drug, containing the proteolytic enzyme *ficin*, is both very efficient and non-toxic. Oil of chenopodium is efficient, but is so highly toxic in effective therapeutic doses that I hesitate to recommend it. The toxic sequelae may not appear for three or four weeks after administration of this drug. If it is prescribed, the patient must be hospitalized and watched very carefully throughout treatment. It should be preceded and followed by saline purgation.

5. *Strongyloidiasis*. Gentian violet is the only drug that has proved effective in this disease. Enteric-coated tablets of gentian violet medicinal, administered in doses of one grain three times daily before meals for a period of approximately 16 days (or until 50 grains have been administered) are recommended. One or two courses of treatment produce cure in the average cases. For refractory patients, we in the Department of Tropical Medicine at Tulane University, and others following our recommendations, have been giving 25 c.c. of a 1 per cent solution of gentian violet by duodenal intubation, and have had very satisfactory results.

6. *Tapeworm infections*. For tapeworms, whether large or small forms, the oleoresin of aspidium is probably the most satisfactory anthelmintic, but the coöperation of the patient and adequate preparation of the patient are important requisites for successful treatment. Carbon tetrachloride is also quite satisfactory. In prescribing either drug, the patient should be hospitalized or under the direct supervision of the physician. Saline purgation the night before treatment is recommended. The drug is given on an empty stomach in the morning. Carbon tetrachloride is given as a single dose of 3 c.c.; the oleoresin of aspidium in three divided doses of 20 minims each, one-half hour apart. Two hours after the administration of either anthelmintic, there should be post-treatment saline purgation, and no food should be permitted until adequate bowel movements have been obtained. There is one additional suggestion. Some physicians prefer intubation of the oleoresin with magnesium sulphate and mucilage of acacia (oleoresin of aspidium, 60-120 minims;  $MgSO_4$ , sat. sol., 30 c.c., mucilage of acacia, 30 c.c.). The drug can be intubated under a fluoroscope in the physician's office and requires no post-treatment purgation.

Before passing on to the third section of the discussion, opportunity is offered for questions.

Question: What has been your experience with pumpkin seeds in the treatment of tapeworms?

Answer: My experience with macerated, shelled pumpkin seeds (either taken en

masse, or after a strained decoction has been administered) has been consistently unsuccessful in the removal of the heads of the worm. In this respect, it parallels the meat of the cocoanut, in evacuating a long portion of the worm but in failure to dislodge the head.

Question: Is caprokol or gentian violet treatment of seatworm infection (oxyuriasis) effective in removing the worms?

Answer: Oxyuriasis is usually a familial or an institutional infection, in which the majority of the group harbor the worms. Treatment of one or two members of the group is useless when the other infected members remain untreated. Hence treatment of all infected members of the group, as determined by repeated cellophane swab examinations, is indicated. Several courses of caprokol by mouth, accompanied by hexylresorcinol solution retention enemas, are frequently necessary to remove all of the seatworms in an infected patient. Gentian violet therapy in this infection is promising and deserves thorough clinical trial.

Question: Is there any specific treatment for trichinosis?

Answer: Chemotherapeutics have all been disappointing and convalescent serum has not been particularly helpful. I know of no treatment for trichinosis except supportive management of the patient and palliative procedures.

#### THE RÔLE OF ANIMAL PARASITES IN PULMONARY DISEASE

Animal parasites may act either directly or indirectly in the production of disease of the respiratory tracts.

1. *As Causative Agents.* *Ascaris*, hookworm and *Strongyloides* larvae in migration through the lungs may cause atypical pneumonia and *Strongyloides* may become established in the bronchial epithelium. Moreover, these organisms may reactivate pulmonary tuberculosis (Bülow, 1929). Amebiasis of the lungs or pleural cavity must be differentiated from pulmonary tuberculosis, pyogenic abscesses of lungs or bronchopneumonia; also from bronchiectasis (Keeton and Hood, 1938). Pulmonary implantation of hydatid cyst is only secondary in incidence to hepatic hydatid. In Japan, Korea, Formosa, certain districts in China and elsewhere in the Orient, semi-encapsulated adults of the pulmonary distome (*Paragonimus westermani*) typically develop in peribronchial sites, with openings into the bronchioles, discharging necrotic tissue debris, blood and eggs of the worm, with an hemoptysis which requires differentiation from that of pulmonary tuberculosis. In the Orient, Africa and Tropical America, adult blood flukes or schistosomes at times become lodged in the pulmonary arterioles, with multiple abscesses or tubercles around their eggs which are infiltrated in the pulmonary parenchyma.

2. *As Indirect Agents.* Freiman (1927) states: "Malaria forms a good soil for the implantation of tuberculosis and . . . the simultaneous presence of both diseases in the same subject increases the gravity of the prognosis." Collari (1932) observes: If tuberculosis gets a foothold in a chronic malaria patient, it tends to be miliary in type. Induced malaria in a tuberculous patient is invariably contraindicated. Boggian (1934) has found that the supervention of malaria in a tuberculous patient lights up and extends latent lesions. Visceral leishmaniasis or kala-azar produces an absolute lympho-

cytosis with a leukopenia. Hence, in this disease, due to greatly lowered resistance of the patient, bronchopneumonia is a common complication.

Are there any questions on the topic of animal parasites in pulmonary disease?

Question: What treatment do you recommend for hookworm, *Strongyloides* and *Ascaris* larvae in the lungs?

Answer: There is no known safe anthelmintic procedure which will kill hookworm or *Ascaris* larvae in the pulmonary vessels or respiratory tree. Specific treatment must be reserved until the worms have arrived in the intestinal tract. *Strongyloides* larvae, like *Strongyloides* adults that have become established in the bronchial epithelium, are killed by gentian violet administered by vein as a filtered one-half per cent solution, given every third day in amounts not in excess of 25 c.c. at each administration. For this treatment the patient must be hospitalized and under the direct supervision of the physician.

Question: How can one distinguish pulmonary distomiasis from tuberculosis of the lungs?

Answer: In pulmonary distomiasis there is typically a rusty-brown tinge to the blood-flecked sputum. Microscopic examination of the discharge reveals the characteristic golden-brown eggs of the parasite, which give the iron-rust appearance to the sputum.

## CASE REPORTS

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### GRANULOCYTOPENIA FROM SULFANILAMIDE WITH UNUSUAL BLOOD CRISIS AND RECOVERY; CASE REPORT \*

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IN an issue of the *Journal of the American Medical Association* there appeared experimental studies, case reports and an editorial concerning sulfanilamide. Two of these papers<sup>1,2</sup> dealt with the leukocytic response to sulfanilamide and its mode of action. In an interesting and cogent extension of the subject were two case reports<sup>3,4</sup> of fatal intoxication following administration of the drug. Reference was made to two other reports of fatal cases. The subject was reviewed editorially, and one is reminded that the Council on Pharmacy and Chemistry originally advised periodical microscopic examinations of blood of patients taking sulfanilamide.

As with any new therapeutic agent, sulfanilamide has been more or less indiscriminately employed in the treatment of almost every type of infection. In the wake of such uncontrolled exploitation there invariably appear reports of mortality and morbidity. Such was true of dinitrophenol, benzedrine sulphate and other drugs.

That sulfanilamide can cripple the hematopoietic mechanism is undeniable. It would seem, however, that the drug is dangerous only to those individuals who may be sensitive to it. It may be compared in this respect to amidopyrine. Its danger, however, is greater because of its more extensive application.

There are, no doubt, many physicians who have observed unusual or pathological blood pictures in patients receiving sulfanilamide. Anemias, principally of the hemolytic type, leukopenic states of varying degrees, as well as peculiar distributions of the granulocytes, all have been reported. Apparently there is no constant hematopoietic response to this drug. This fact further emphasizes the necessity of watching closely the blood reaction of any patient taking such medication.

The case I wish to report presents two interesting features aside from the polymorphonuclear leukopenia and the anemia. One is the apparent life saving effect of daily transfusions, and the other is the very unusual crisis, not unlike the crisis of pneumonia, which occurred during the treatment.

#### CASE REPORT

The patient, a white female, aged 41, was first ill with a sore throat, not unlike others that were prevalent during the winter season in this vicinity. Having had a pharyngitis a few months before, which was relatively mild and for which she was given sulfanilamide by her physician, she began taking the drug again without her

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doctor's prescription. The infection began as a sore throat with a slight elevation of temperature and headache. During the first three days she took 5 grains of sulfanilamide every four hours. On the evening of the third day the temperature was recorded as 104.2° F. At this time she was seen by her physician who prescribed 10 grains of sulfanilamide every three hours for two days. Also, on the evening of the third day and morning of the fourth, the patient became conscious of a sore mouth and slight bleeding from her gums. The temperature continued to rise and on the fifth and sixth days reached 106° F. On the sixth, seventh and eighth days she received 90 grains more of sulfanilamide, making a total of 300 grains. Because of the continued high temperature and bleeding gums, which showed several areas of gangrenous ulceration as also did the hard and soft palates, the patient was admitted to the Medical Arts Hospital.

When first seen in the hospital, there was noticed marked blueness of the lips and nails. The patient was obviously quite ill. She complained chiefly of her mouth, marked dizziness and faintness. Examination revealed marked congestion of the gums with small hemorrhagic areas. There were two large gangrenous areas noted on the upper gum. There were several smaller ulcerations on the roof of the mouth and two or three similar areas on the left tonsil. The pharynx was moderately congested. There was one small gland under the left jaw, and two or three small ones in the right anterior cervical region. The patient, although not truly stuporous, was extremely non-communicative and apparently a victim of considerable prostration. Her temperature on admission to hospital was 104° F., pulse 130, and respiration 22. Her blood pressure was 135 systolic and 90 diastolic. There were no other notable physical findings.

The blood count on admission to the hospital showed 2,680,000 red blood cells and 42 per cent hemoglobin. There were 1,800 leukocytes, of which 4 per cent were polymorphonuclear cells, 1 per cent mononuclear leukocytes, and 95 per cent lymphocytes. The patient was given an immediate transfusion of 300 c.c. of whole blood. On the following day her blood count revealed 3,040,000 red cells, 45 per cent hemoglobin, and 4,150 leukocytes of which 1 per cent were polymorphonuclear cells and 99 per cent were lymphocytes. The patient was transfused daily, averaging 300 c.c. of whole blood with each transfusion. Her condition continued as previously described, temperature ranging from 101° F. to 104° F., and pulse ranging from 120 to 130. The lesions in her mouth and throat remained unchanged during the first several days of her hospitalization. Her responsiveness was likewise unaltered, inasmuch as she remained very quiet and listless. On the sixth day her red cell count was 3,510,000. There were 3,250 white cells, 9 per cent of which were polymorphonuclear cells, and 6 per cent of which were young forms. On the seventh day the white count remained approximately the same, except that 13 per cent of the white cells were of juvenile type. On the eighth day there was a remarkable crisis. This crisis was characterized by a critical drop in her temperature to a subnormal level. Simultaneously, that is within a few hours, a blood count revealed a red cell count of 3,750,000, and 10,400 white cells, 25 per cent of which were polymorphonuclear cells, 6 per cent of the polymorphonuclear cells being young forms. From this point on, the patient showed consistent improvement, the white cells rising on the tenth day to a peak of 19,350, 54 per cent of which were polymorphonuclear cells. Following this, her count dropped to 10,000 odd white cells and on down to 8,300, at which level she fluctuated with a perfectly normal differential picture. Her temperature rose from a subnormal level to a normal one and remained there during the rest of her residence in the hospital. No other therapy was employed except daily blood transfusions.

As intimated in the first part of this case report, the progress of this patient is reported because of the unusual crisis that she experienced, associated with a simultaneous rise in her white cell count; and because of the apparent effectiveness of daily

transfusions. The crisis described was quite similar to the crisis observed in pneumonia, and one that I have never before observed in a blood dyscrasia.

#### COMMENT

A case of sulfanilamide intoxication has been reported which shows an unusual leukopenia of a polymorphonuclear type. The picture as first seen had many characteristics of a typical Schultz agranulocytic angina. Because of the history of sulfanilamide medication, a tentative diagnosis of sulfanilamide intoxication was made and daily transfusions were given. There were noted, after about seven days, a critical drop in temperature and simultaneous rise in the polymorphonuclear leukocytes. The purpose of this report is to emphasize the apparent value of daily blood transfusions in suspected sulfanilamide intoxication, and the necessity of periodic microscopic blood examinations.

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### EXFOLIATIVE DERMATITIS DUE TO PHENOBARBITAL WITH FATAL OUTCOME; REPORT OF TWO CASES \*

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PHENOBARBITAL, chemically a white colorless substance, phenylethylbarbituric acid or phenylethylmalonylurea was first placed in the hands of clinicians in 1911 under the proprietary name of Luminal. Introduced as a sedative and hypnotic, its greatest success was in the treatment of epilepsy; and, at the present time, it is probably the most frequently prescribed sedative in modern medical practice.

A few months after its introduction, Loewe<sup>1</sup> (1912) reported the first case of cutaneous reaction due to the ingestion of phenobarbital. He published his observations of three cases, each patient exhibiting a generalized macular eruption, without systemic reaction, the rash fading upon withdrawal of the drug. The literature reveals few additional reports until Heuber<sup>2</sup> (1919) reported the development of a hemorrhagic type of cutaneous eruption allegedly due to phenobarbital medication. Weber<sup>3</sup> (1925) described a case presenting large bullae associated with jaundice, and Hamilton et al.<sup>4</sup> (1926) reported the first case of a universal exfoliative dermatitis due to phenobarbital. In this case the

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patient recovered after a protracted illness, with complete exfoliation including the nails, hair and mucous membranes.

Following the excellent summary of the symptomatology of phenobarbital poisoning by Menninger<sup>5</sup> (1928), in which he collected from the literature only 41 cases of cutaneous eruption due to phenobarbital therapy, a large increase in the number of case reports was noted. Numerous articles were published with every possible type of eruption and all of the cases terminated in complete recovery. Chavany and Vannier<sup>6</sup> (1929) reported the first fatality. They reported two deaths. Their first case was a 30 year old white female who had taken phenobarbital 0.1 gram for nine days before the appearance of the eruption. The patient developed a generalized exfoliative dermatitis with high temperature, increased pulse rate, marked oliguria, and a severe toxemia resulting in death the sixth day of her illness. Autopsy findings showed only a severe congestion of the parenchymatous organs. The second case followed shortly after the preceding fatality. This was a 48 year old white female who had been taking phenobarbital for six months. The dosage had been increased up to 0.6 gram daily prior to entering the hospital. A generalized exfoliative dermatitis developed including the mucous membranes, and the clinical course followed the first case very closely. Death occurred seven days after hospitalization and eleven days after the onset of the eruption. Autopsy findings were not greatly different nor more enlightening than in the first case.

Brunsting<sup>7</sup> (1932) reported seeing a patient on the fifth day of her eruption with a history of having taken a phenobarbital preparation in the amount of one-quarter grain three times daily for ten days. The eruption resembled an acute erythema multiforme, and the clinical course simulated a fulminating pemphigus. Death occurred on the fifteenth day and evidence that phenobarbital was the sole precipitating factor was declared to be only circumstantial.

Millard<sup>8</sup> (1933) reported several cases of dermatitis due to phenobarbital, one terminating fatally. This patient was a 61 year old white male who was given Theominal (phenobarbital one-half grain) three times daily for 18 days. The resulting dermatitis was of a universal exfoliative type, resembling an arsenical dermatitis, and involving the mucous membranes. Autopsy findings showed a bronchopneumonia and chronic nephritis; no arsenic was found post mortem.

Heckmann<sup>9</sup> (1935) reported a fatal case in a five and one-half year old white child being treated with Luminal for an epilepsy of one year's duration. The medication was given in 0.05 gram doses twice daily for from 15 to 17 days before mouth and cutaneous lesions made their appearance. The clinical course was marked by a rather high temperature, evidence of a severe toxemia, and the formation of large bullae with generalized exfoliation including the hair. The patient died on the fourth day of hospitalization; autopsy findings were not significant.

A fatal case was recorded by Scarlett and Macnab<sup>10</sup> (1935) in which the patient, a 17 year old female, was hospitalized because of an acute encephalitis. She was given phenobarbital 1.5 grains at bedtime after hospitalization of one week and at a time when the acute process was apparently resolving. After 12 days on this medication, the patient developed a fever followed by a red macular eruption which rapidly became worse, and which was accompanied by a necrosing stomatitis and rhinitis. Death occurred six days after the onset of

the eruption and autopsy revealed, in addition to the dermatitis, a cloudy swelling of the kidneys and liver, and numerous small and one large hemorrhage in the brain and its covering, indicative of a hemorrhagic encephalitis.

Sweitzer and Laymon<sup>11</sup> (1937) reported four cases of cutaneous reaction due to barbituric acid derivatives, of which three terminated fatally. Their first case, a 48 year old white female, was given one and one-half grains of phenobarbital for approximately three weeks, at which time a red itchy eruption made its appearance. The eruption, at the time of hospitalization two weeks later, was universal except for the palms and soles, red, scaling and accompanied by an increased temperature, pulse and respiration. The patient died after 12 days of hospitalization and autopsy findings showed the presence of gall stones, fatty changes in the liver and terminal bronchopneumonia in addition to the exfoliative dermatitis.

Their second case was 58 years of age, and was hospitalized because of coronary sclerosis, auricular fibrillation and a possible lung infarct. Butyl-ethyl barbituric acid (three grains) daily was given the patient for approximately 50 days. Vesicular lesions later becoming almost hemorrhagic, together with a red and swollen throat, comprised the dermatologic picture, accompanied by an agranulocytosis of marked degree. An autopsy was refused.

The third fatality was a white female 67 years of age who had been given sodium pentobarbital for ten days. A red pruritic cutaneous eruption appeared the fourth day after medication was initiated, and, due to discomfort, the medication was continued prior to hospitalization. The patient died after five days in the hospital, having developed an anuria, edema of the extremities and a terminal pulmonary edema. An autopsy was not obtained.

Because of the comparative rarity of such cases, and with the view also in mind of bringing to the attention of the medical profession the possible dangers of phenobarbital medication, a summary of two fatal cases observed at the University Hospital is presented.

#### CASE REPORTS

*Case 1.* C. R., a white male, aged 48, dentist, was admitted to the University Hospital, February 20, 1934, with a chief complaint of general weakness and difficulty in breathing. The patient had noticed a moderate generalized weakness for three or four months with labored breathing on exertion, and an increase in the symptoms the two weeks prior to entering the hospital. He had also noticed a nervousness which he ascribed to financial and business difficulties. His past history was not suggestive of serious illness.

Physical examination showed the patient to be a well developed and well nourished middle-aged white male with a rather apprehensive appearance. The breathing was somewhat labored but not increased in rate. There was no clubbing of the fingers. The skin was of normal color and texture. The eyes reacted normally; the nose and throat appeared normal. The oral cavity showed some carious lower teeth, the upper jaw being edentulous. The thyroid was normal. The thorax was symmetrical and without external abnormalities. The heart was not enlarged to percussion, the rate and rhythm normal with no murmurs heard. Blood pressure was 125 mm. systolic and 70 mm. diastolic. The lung fields were clear to percussion and auscultation with equal and ample excursion. The abdomen presented no masses or tender areas; the spleen and liver were not enlarged. The extremities presented no change except a slight tremor of the fingers. Rectal examination showed a few external hemorrhoids; the genitalia were normal. The deep and superficial reflexes were physiologically normal.

The patient was seen by the Department of Neurology, who found no organic disease present. The Department of Neuropsychiatry made a diagnosis of a psychoneurosis with fatigue reaction in a compulsive type of individual.

The laboratory findings were as follows: urine examination was normal. The blood count showed: hemoglobin 89 per cent (Sahli); red blood cells 4,500,000; white blood cells 10,150; differential count: polymorphonuclear leukocytes 72 per cent; lymphocytes 23 per cent; monocytes 4 per cent; basophiles 1 per cent. Stool examination for blood and parasites was negative. A specimen of sputum showed no acid-fast bacilli, but spirochetes were found to average two per high power field. Frontal stereoscopic examination of the thorax was done February 21, 1934, with the following reading: moderate peritruncal infiltration, somewhat generalized, more prominent in the region of the right lower stem bronchus. An electrocardiogram taken February 23, 1934 was normal.

Medication was symptomatic and was given in the form of luminal one-half grain three times a day and one and one-half grains at bed-time. He was also given 0.25 c.c. adrenalin solution without effect on his moderately dyspneic breathing. He was discharged March 2, 1934, with a prescription for luminal to be taken if necessary for rest. The total amount of luminal taken in the Hospital was 28.5 grains.

The patient was readmitted March 15, 1934, in a semi-comatose condition. The history revealed that immediately after discharge, March 2, 1934, he developed a fever with the appearance of red "blotches" about the face which gradually spread to the trunk and extremities. Accompanying the cutaneous eruption the patient developed a sore mouth and throat, so severe that no food or liquid had been taken for a period of four days. The wife stated that one luminal tablet (0.032 gm.) was given three times daily since leaving the hospital and continued until four days before admittance. (Total of 13.5 grains luminal taken at home.)

Physical examination on admission March 15, 1934, revealed the patient to be acutely ill with a rectal temperature of 103° F., pulse of 100, and with a generalized cutaneous eruption consisting of erythematous maculo-papular patches showing a tendency to confluence. This was especially true about the face and arms, where marked exfoliation was seen (figures 1 and 2). Pitting edema was present not only in the lower extremities but also about the trunk and upper extremities. The mucous membranes showed large vesicles, for the most part ruptured, leaving denuded surfaces covered with a whitish muco-fibrinous material. The lips were swollen, edematous and fissured; swallowing was accomplished with great difficulty.

The patient was placed on a regime of saline purgations, colloidal baths, intravenous sodium thiosulphate and large amounts of intravenous glucose and sodium chloride solutions. He continued to run a septic type of fever ranging between 101° F. and 105° F., pulse rate from 90 to 130 per minute and respirations from 15 to 30. The semi-comatose state present on admission continued until March 19, 1934, at which time considerable clearing of the mental faculties was noted. There were no abnormal physical findings except the cutaneous eruption and the fever.

A roentgen-ray film of the chest taken March 16, 1934, showed a peritruncal infiltration of both bases, predominantly right, and definite increase in density over the previous films taken February 21, 1934. The urinary output, at first suppressed, rose to normal amount with no abnormal findings on repeated examination. The blood picture was within normal limits except during the last two days when the following blood picture was found: hemoglobin 75 per cent (Sahli); red blood cells 4,150,000; white blood cells 24,000; polymorphonuclear leukocytes 94 per cent; basophiles 2 per cent; lymphocytes 1 per cent; monocytes 2 per cent; myelocytes 1 per cent. A blood culture was negative. Stool examinations were negative. Repeated sputum examinations revealed no acid-fast organisms or spirochetes, but did show numerous encapsulated lanceolate diplococci.



FIG. 1. Case 1, C. R., appearance of eruption at time of admission, February 20, of a maculo-papular type and tending to become confluent.

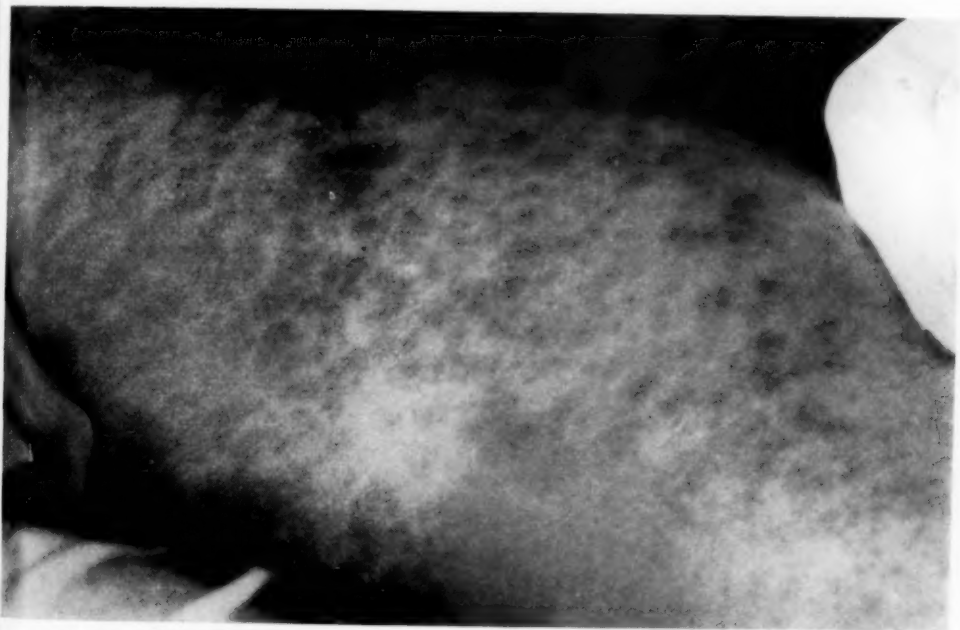


FIG. 2. Case 1, C. R., close-up view of eruption taken the same date as figure 1.

The cutaneous eruption soon became universal with a marked exfoliation but without vesiculation or bullae. The mouth and throat lesions became progressively more numerous. A roentgenogram taken March 20, 1934, showed an extensive broncho-pneumonia bilaterally and the condition of the patient became progressively worse, respirations ceasing March 21, 1934.

A limited autopsy was permitted and the principal findings in addition to the universal exfoliative dermatitis were a right-sided cardiac dilatation, bronchopneumonia, acute bilateral purulent bronchitis, and marked subendocardial fatty infiltration.

*Case 2.* E. C., a 45 year old white male, roofer by occupation, was admitted to the University Hospital, May 7, 1937, complaining of a cough, "chest trouble," and a skin eruption. About six weeks prior to admittance to the hospital the patient contracted a cold, accompanied by a temperature of 102°, muscle and joint pains, cough and pain in the chest. Work was attempted after a two week convalescence, but all previous symptoms recurred, especially the productive cough. He was treated by his physician and the medication consisted of six white tablets and eight capsules daily for about two weeks. (This was later found to be phenobarbital one-half grain and ephedrine sulphate capsules three-eighths grain respectively.) Six days before coming to the hospital the temperature rose to 103° F., the general condition became much worse, and a "spotty rash" developed on the extremities, trunk and face, which was rapidly becoming more extensive.

Physical examination showed the patient to be acutely ill with a temperature of 103° F., pulse 120, and respirations 24. He presented an extensive generalized erythematous maculo-papular eruption which spared only the palms, soles and scalp. The patches were penny to palm-sized with a tendency toward confluence, of a reddish-brown to a reddish-purple color, blanched on pressure, and without sharp demarcation fading off into the normal skin. The most marked involvement was seen over the back, the anterior thigh surfaces showing the least. The genitalia were markedly erythematous and edematous with a patchy superficial denudation of the epithelial covering of the scrotum. Numerous vesicles were present about the vermillion and mucous surface of the lips and throughout the oral cavity and pharynx. The cervical glands were enlarged as were the left axillary glands. The heart rate was rapid but there were no murmurs heard nor any irregularity of rate or rhythm. The blood pressure was 124 mm. systolic and 74 mm. diastolic. The left lung base posteriorly was slightly dull to percussion and auscultation revealed coarse râles over both bases and in the axillae, but there was no increased transmission of breath or voice sounds. Tactile fremitus was normal. Percussion and palpation of the abdomen revealed no splenic or liver enlargement. The inguinal glands were olive-sized, discrete, firm and non-tender. The superficial and deep reflexes were active and equal. Rectal examination showed a prostate of normal size and consistency.

Laboratory examination showed the blood Kahn reaction to be negative; urine examination was normal. Tests for iodides and bromides in the urine were negative. A blood count taken on May 7, 1937, showed a normal hemoglobin and red cell count with a white blood count of 17,350. On May 11, 1937, the white cell count had dropped to 7,000 with a differential count of polymorphonuclear leukocytes, 88 per cent, lymphocytes 12 per cent, and further drop was noted on May 13, to 6,000 white blood cells with a similar cell distribution. Sputum examination was negative for acid-fast bacilli and spirochetes. Blood culture showed no growth. Blood non-protein nitrogen was 27.2 mg. per cent. Stereoscopic films taken May 7 revealed a calcareous parenchymatous scar of the right apex, bilateral minimal calcareous peribronchial adenopathy, and residual peritruncal infiltration, left inferior lobe with obliterative pleuritis.

The patient was given frequent colloid baths, intravenous sodium thiosulphate and large amounts of intravenous glucose and normal saline infusions. His chronic respiratory infection was treated with inhalations, expectorants and mild sedatives. The

cutaneous reaction remained stationary until May 10 when new small and large vesicles and bullae appeared on the trunk and extremities. By May 12, the eruption became almost universal, the palms, soles and a small patch on the anterior surface of each thigh remaining uninvolved. Throughout hospitalization the temperature remained septic in character, ranging between 100° and 104° F., and on May 12 definite signs of bronchopneumonia were elicited. The patient became progressively weaker and death occurred May 14, 1937.

An autopsy substantiated the clinical findings. In addition to the bilateral lobular pneumonia and almost universal bullous, ulcerative and exfoliative dermatitis, the findings included an acute diphtheritic laryngitis and esophagitis, and an acute passive congestion and degeneration of all parenchymatous organs.

#### COMMENTS

A review of the literature reveals an increasing incidence of reactions from the use of the barbiturates in therapy.

The recorded fatal cutaneous eruptions from phenobarbital therapy are few in number but it is believed numerous others have been observed, allowed to go undiagnosed, or if recognized, mentioned incidentally or not at all in the literature.

The characteristic eruption due to phenobarbital medication in the more severe cases may be differentiated from the maculo-papular eruption due to the basic coal-tar derivatives which do not proceed to the stage of vesiculation and exfoliation.

It is believed that the medical profession as a whole should be aware of the dangers of the indiscriminate use of the barbiturates, and that possible serious reactions may occur when treating patients with repeated daily administrations of the various derivatives of the group.

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# SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS; REPORT OF AN ADDITIONAL CASE \*

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INTERSTITIAL emphysema of the lungs following injury or greatly increased intrapulmonary pressure has long been recognized clinically by the appearance of air in the subcutaneous tissues about the neck. The term surgical emphysema has been applied to this condition to distinguish it from vesicular emphysema produced by bronchial obstruction and subsequent dilatation of the pulmonary alveoli. The first description of interstitial emphysema occurring spontaneously, that is, without trauma or greatly increased intrapulmonary pressure, was recorded by Hamman<sup>1</sup> in 1937. He reported six cases and described a new physical sign characteristic of the condition. He emphasized that spontaneous interstitial emphysema is probably commonly overlooked because of the similarity of its symptomatology to that of other well known diseases.

SUMMARY OF CASES OF SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNGS

Case No.	Age	Sex	Occupation	History	Subcutaneous Emphysema	Roentgenogram	Duration of illness
1	51	Male	Physician	Sharp pain in chest for one hour.	Absent	Normal	2 weeks
2	17	Male	Tin worker	Substernal pain, swelling above clavicles, dysphagia, painful breathing for several hours.	Present above both clavicles.	Not done	Less than 4 weeks
3	25	Male	Physician	Pain in left side of chest. Crackling sensation in region of heart.	Absent	Normal	10 days
4	34	Male	Not given	Substernal pain, choking sensation, "noises in heart" 2 hours.	Absent	Small pneumothorax left apex.	2 weeks
5	29	Male	Salesman	Severe pain in left side of chest.	Absent	Small pneumothorax on left.	3 weeks
6	16	Male	Student	Severe pain in right side of chest for ten minutes.	Present above both clavicles.	Air in anterior mediastinum.	18 days
7	27	Male	Laborer	Sharp pain in left side of chest for one hour. Dyspnea, weakness, noise in chest.	Absent	Small pneumothorax on left. Fluoroscopy showed air in anterior mediastinum	3 weeks

The first six cases were reported by Hamman, the seventh is that of the author.

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Since the six cases reported by Hamman no others have been recorded in the literature so far as I have been able to find. His cases are summarized in the table together with an original case.

#### CASE REPORT

A laborer, aged 27, came to the clinic of the Atlanta Tuberculosis Association on July 25, 1938, complaining of a peculiar noise in his chest. About two weeks previously, while rolling an empty wheelbarrow, he had been suddenly seized with a sharp pain in the left side of his chest over his heart. The pain was knife-like in quality and so severe that he thought he was going to faint. Shortly after the onset of pain he felt a sensation of tightness substernally and became short of breath. His companions told him he was pale and blue. On reaching home about an hour later the pain was less intense and he was able to breathe with only slight difficulty. On getting in bed and turning on his left side he experienced a grinding crunching sensation in the region of his heart. Standing at least a yard from the patient, his wife heard what she described as a noise "like the wadding up of paper." This sound was heard by several other members of his family. Aside from the discomfort from the peculiar sensation there was no increase in the pain while the sensation was present. After a day in bed, only slight soreness in the left side of the chest and moderate dyspnea were present. He was able to return to his work as a laborer the following day. The crunching sound and sensation, however, remained, though somewhat abated, until his admission to the clinic. At that time he had no pain but was still short of breath on exertion.

The patient was a rather thin undernourished young white man not appearing ill. There were signs of a small pneumothorax in the left axilla. The area of cardiac dullness was normal in position and extent, the sounds were of good quality with a faint systolic murmur at the apex. On turning the patient on his left side there appeared a crunching, crackling, slapping sound synchronous with the heart beat. The sound was clearly heard with the bare ear a foot from the patient. It was accentuated on expiration and diminished on inspiration, disappearing entirely when the patient turned from the left side.

His temperature was 98.6°; a complete blood count and urinalysis were normal. The blood pressure was 130 systolic, 80 diastolic. The tuberculin test, using first strength (0.01 mg.) Purified Protein Derivative intradermally, gave a moderately positive reaction. A roentgenogram of the chest showed a small area of pneumothorax on the left with about 10 per cent collapse of the lung. Fluoroscopic examination demonstrated several bubbles of air in the tissues between the anterior surface of the heart and the chest wall and between the diaphragm and the pericardium. With the production of the peculiar noise the bubbles of air between the heart and anterior chest wall changed shape with each movement of the heart and lungs.

The patient was given a cough mixture and was put to bed for a week. At the end of this time he reported that the dyspnea and crunching sensation had disappeared. Fluoroscopic examination at this visit was entirely negative. Three weeks after admission to the clinic he returned to work and has felt well since. A roentgenogram taken Sept. 2, 1938, was reported normal.

#### COMMENT

The mechanism by which the air reaches the mediastinum has been postulated by Hamman who wrote:

I am convinced that not infrequently pulmonary alveoli must rupture and air escape into the interstitial tissues of the lung. If only a small amount of air escapes

no symptoms may appear or perhaps only localized pain. This condition may account for some of the many transient pains in the chest of which patients complain and for which no cause can be discovered. If a larger amount of air escapes it may travel along the interstitial bands to the pleura and there form a vesicle; the pleural membrane over the vesicle is stretched and often ruptures. This seems to me the most reasonable explanation for the occurrence of spontaneous pneumothorax. At other times the air spreads along the interstitial bands toward the hilum and escapes into the mediastinum, infiltrating the mediastinal tissues which lie between the heart and anterior chest wall and often escaping into the subcutaneous tissues of the neck. The symptoms then produced are severe and may closely simulate the symptoms of coronary occlusion or of pericarditis.

In cases of spontaneous interstitial emphysema there is a sudden onset of a sharp pain in the chest which may be accompanied by a choking sensation, dyspnea and a feeling of tightness substernally. Occasionally swelling above the clavicles will be noted by the patient. The pain is usually severe at the time of its first appearance, then gradually diminishes in intensity until it disappears, usually within one or two hours after the onset. Often the patient will notice a peculiar crunching noise or sensation in his chest. This phenomenon frequently is present only when a certain posture is assumed and in some cases the pain will be intensified with its appearance. The symptoms of this condition are, as has been pointed out, similar to those seen in a variety of diseases, notably coronary artery disease and pericarditis. In these diseases, however, there is more likelihood of a severe constitutional reaction resulting from myocardial disturbance and shock.

On physical examination one may find subcutaneous emphysema in the neck. The area of cardiac dullness may be diminished in extent or even absent. Signs of a pneumothorax may be present. Often a loud crunching, grinding, crackling sound synchronous with the heart beat can be heard some distance from the chest wall. This sign, first described by Hamman, is characteristic of interstitial emphysema and is unlike the so-called "cardiac knock" or "systolic râles" which are sometimes heard over the heart in cases of pneumothorax or atelectasis. In some cases air may be demonstrated in the mediastinal tissues by fluoroscopic examination or by a roentgenogram.

Once the diagnosis is established the patient may be treated symptomatically and reassured as to the favorable prognosis, for the symptoms soon disappear, leaving him apparently as well as before. When recovery is complete there is no indication to curtail his activities in any way.

*Note:* Since this case was reported another typical case of spontaneous interstitial emphysema has been observed by the author.

#### REFERENCE

1. HAMMAN, LOUIS: Spontaneous interstitial emphysema of the lungs, *Trans. Assoc. Am. Phys.*, 1937, lii, 311-319.

## EDITORIAL

### INTESTINAL STASIS AND MACROCYTIC ANEMIA

IN 1895 Faber<sup>1</sup> in Denmark first called attention to the association of pernicious anemia with a stricture of the small intestine. He postulated that absorption of a poison from the stagnant bowel contents above the stricture was responsible for the anemia. Meulengracht<sup>2</sup> added weight to this theory in 1921 when he found at the autopsy of a case of severe "pernicious anemia" associated with a tuberculous stricture of the ileum that the entire small intestine was heavily infected with bacteria. Comparing his case with five similar cases previously reported he arrived at the following conclusions: (1) pernicious anemia may develop on the basis of benign intestinal strictures; (2) the anemia is probably due to the absorption of hemotoxic substances from the dilated and infected portion of the bowel above the stricture; (3) such cases support the theory of the intestinal origin of cryptogenetic pernicious anemia.

Several years later these clinical observations received experimental support when Seyderhelm<sup>3</sup> and his associates succeeded in simulating the clinical and pathologic picture of stricture anemia in four of ten dogs in which they had produced intestinal strictures at operation. Later Horster<sup>4</sup> added further experimental evidence along the same lines by producing severe anemia associated with indicanuria and hemosiderin deposits in the liver and spleen in dogs with intestinal strictures or blind pouches which he had created at operation. The symptoms cleared up after resection of the blind pouch or stricture.

Seyderhelm was the first to report recovery from pernicious anemia in a patient after resection of an intestinal stricture. He has also recorded two instances of striking improvement in patients with pernicious anemia following the institution of ileostomy to afford better drainage of the bacteria-infested small intestine. Dixon<sup>5</sup> and his associates in this country have observed a similar response to ileostomy in certain patients suffering from pernicious anemia. These observations all fitted in well with Meulengracht's original concept of the etiology of pernicious anemia.

Then with the discovery of liver therapy for pernicious anemia by Minot and Murphy in 1926, soon to be followed by Castle's fundamental observations on the relation of the intrinsic (gastric) and extrinsic (food) factors

<sup>1</sup> FABER, K.: *Perniciöse Anämie bei Dünndarmstrikturen*, Berlin. klin. Wchnschr., 1897, xxxiv, 643-646. (Case previously published in Danish literature, 1895.)

<sup>2</sup> MEULENGRACHT, E.: *Darmstriktur und perniziöse Anämie*, Arch. f. Verdauungskr., 1921, xxviii, 216-225.

<sup>3</sup> SEYDERHELM, R., LEHMANN, W., and WICHELS, P.: *Intestinale perniziöse Anämie beim Hund durch experimentelle Dünndarmstriktur*, Krankheitsforschung, 1927, iv, 263-279.

<sup>4</sup> HORSTER, H.: *Experimentelle Therapie bei intestinaler Autointoxication*, Ztschr. f. d. ges. exper. Med., 1935, xcv, 514-518.

<sup>5</sup> DIXON, C. F., BURNS, J. G., and GIFFIN, H. Z.: *Pernicious anemia following ileostomy*, Jr. Am. Med. Assoc., 1925, lxxxv, 17-20.

to the hematopoietic principle contained in liver, the toxic theory gave way to the overwhelming evidence that pernicious anemia was a deficiency disease, or at least a "conditioned deficiency state." However, the exact mechanism of action of the liver principle is still a mystery. The possibility exists that this principle may act, not as a mere building-stone for the proper maturation of the erythrocytes, but conceivably by promoting the detoxification of injurious substances absorbed from the intestinal tract.

In an attempt to examine this hypothesis more carefully, Barker and Hummel<sup>6</sup> have recently reviewed 51 cases of macrocytic anemia in association with intestinal strictures and anastomoses. The macrocytic anemia in these patients differed from so-called idiopathic pernicious anemia in several respects, namely: the presence of free hydrochloric acid in the gastric juice of nearly 50 per cent of the cases, the demonstration of intrinsic factor in the gastric juice of several patients, and the relative infrequency of neurologic manifestations. That the relationship between the macrocytic anemia and the intestinal lesion was more than a coincidental one was definitely established in the six cases in which surgical correction of the intestinal abnormality was followed by disappearance of the anemia without the aid of liver therapy. Other patients in the series responded sufficiently well to liver therapy to render operative interference unnecessary.

The clinical picture presented by this group of cases more closely resembles sprue than true pernicious anemia, yet in those cases in which tests of intestinal absorption were carried out the striking impairment in intestinal absorption so characteristic of sprue was not noted. The anemia seemed to be intimately bound up with stagnation and putrefaction of the contents of the small intestine, either above strictures or in blind loops created by anastomoses. Two possible explanations for the production of the anemia were suggested: (1) the increased bacterial activity in the intestinal tract leads to the destruction of hematopoietic material before it can be assimilated; (2) the increased absorption of hemotoxic products of bacterial putrefaction gives rise to the anemia through the direct action of these toxins on the blood, bone-marrow, or even the liver. It was impossible to determine which of these two mechanisms might be playing the major rôle. At any rate, the anemia could be alleviated either by removing surgically the cause for stagnation or by supplying an excess of the liver principle. If the toxic theory be correct, then "stricture anemia" may be regarded as a condition in which the body is unable to supply sufficiently large amounts of detoxifying principle (liver principle) to neutralize the excess of toxins absorbed. The development of true "idiopathic" pernicious anemia on the other hand might depend upon the failure of the body (through lack of intrinsic factor) to synthesize the detoxifying principle in sufficient amounts to neutralize the toxic substances normally absorbed from an intestinal tract where stagnation is not necessarily a factor.

<sup>6</sup> BARKER, W. H., and HUMMEL, L. E.: Macrocytic anemia in association with intestinal strictures and anastomoses, *Bull. Johns Hopkins Hosp.*, 1939, lxiv, 215-256.

## REVIEWS

*Sterility and Impaired Fertility.* By CEDRIC LANE-ROBERTS, M.S., F.R.C.S., F.R.C.O.G., ALBERT SHARMAN, M.D., M.R.C.O.G., KENNETH WALKER, F.R.C.S., B. P. WIESNER, D.Sc., Ph.D., F.R.S.E. with a foreword by the Rt. Hon. LORD HORDER, G.C.V.O., M.D., F.R.C.P. 419 pages; 22.5 × 14.5 cm. Paul B. Hoeber, Inc., New York. 1939. Price, \$5.50.

During the past decade real progress has been made in the study of the physiology of the generative organs and much attention has been given to the consideration of sterility. Indeed, the publications on the scientific and practical aspects of sterility and impaired fertility have been so numerous that it has become difficult for even those especially interested in these subjects to be thoroughly conversant with all the literature. Hence it is that such a comprehensive treatise on these subjects as had been written by Lane-Roberts and his three associate authors should be enthusiastically received by the medical profession.

There are eight chapters to this book but it falls rather naturally into three parts. The first covers the general problem of sterility. The second deals with the part played by the male and emphasizes that in a high percentage of instances it is the husband that is responsible for the lack of offspring. The third part of the book is devoted to the gynecological aspects of sterility.

Considerable attention is given to the chemical and morphological examination of semen. The rôle played by the endocrine glands in the control of the reproductive organs is thoroughly covered but in doing this the authors have not passed over the mechanical factors in sterility.

There are references in the appended bibliography to over three hundred articles on sterility and impaired fertility and an appendix which covers many case reports. The genito-urinary specialist, the gynecologist, the man working in the laboratory on problems related to sterility and the general practitioner can all profit from reading this book.

L. B.

*The Practice of Allergy.* By WARREN T. VAUGHN, M.D. 1st. Ed. 1082 pages; 26.5 × 17.5 cm. The C. V. Mosby Co., St. Louis. 1939. Price, \$11.50.

As usual, Dr. Vaughn has written a scholarly book, demonstrating again his wide knowledge of the subject under consideration. The format of the book is attractive in appearance. There are numerous, excellent illustrations which add materially to the text.

Dr. Vaughn has divided his book into 16 parts. It begins with a section outlining the steps in the development of our present understanding of clinical allergy; the general characteristics of clinical allergy, such as the incidence and the effect of climate and heredity, are considered. The next section is on the physiology of allergy and then in order are presented: allergic diagnoses, diagnosis and treatment of food allergy, food allergens, pollens and pollenosis and other inhalant allergy; bacteria and fungi; entomogenous and percutaneous or diadermal allergy; anaphylactic shock; contact allergy; physical allergy; pharmacology; and last, the allergic diseases.

The section on fungi and the section on food allergies are very complete and should be of great value. The botanical classification of foods is presented and a workable classification of fungi, commonly met with clinically, is also given.

Careful and thorough reading impresses the reviewer again with the vast amount of information upon the subject of allergy that Dr. Vaughn has brought together in this book. However, in certain respects the book leaves a sense of dissatisfaction.

First, the arrangement seems faulty in that certain things are overstressed, perhaps at the expense of others that should receive more attention. As an evidence of this, the leukopenic index is given 17 pages, whereas the discussion of the entire subject of skin testing occupies only 22 pages.

Again, Dr. Vaughn discusses very exhaustively the subject of "Diet Diaries" as a diagnostic step in food allergy, giving the impression that they are most helpful in a considerable percentage of cases. The reviewer's experience with this procedure over a period of years has been much less satisfactory, and hence this section appears to him to be tinged with undue optimism. Furthermore, Dr. Vaughn, in the earlier portions of his book philosophizes a great deal about the subject of allergy, and such speculative material appears of doubtful value in a book offered as a standard text.

In the main, certain methods of approach have been developed for books covering given fields of medicine and these methods are adhered to almost without exception by authors of text books.

In this regard, it is the reviewer's opinion that the best plan for the discussion of the subject of allergy that has been developed to date, is that which first covers the general principles; second, the etiologic groups with a discussion of their group characteristics; and third, the clinical conditions encountered in allergy. In the interest of clarity and uniformity this usual arrangement offers advantages over that adopted by Dr. Vaughn.

As a reference book, "The Practice of Allergy" can be highly recommended; as a text book, emphasizing evenly the different aspects of the subject, it can not be accorded the same warm reception.

H. B.

*Textbook of Pathology—A Correlation of Clinical Observations and Pathological Findings.* By CHARLES W. DUVAL, Professor of Pathology and Bacteriology, Tulane University School of Medicine, Chief Visiting Pathologist, Charity Hospital, New Orleans, and HERBERT J. SCHATTENBERG, Associate Professor of Pathology and Bacteriology, Tulane University School of Medicine, Visiting Pathologist, Charity Hospital, New Orleans. 681 pages, 383 illustrations, 13 colored plates; 25 × 17 cm. D. Appleton-Century Co., Inc., New York. 1939. Price, \$8.50.

This one volume text of Pathology appears as a competitor in a field already well stocked with sound standard works which are being periodically revised. The subtitle of the book may offer an excuse for such a volume, but there is nothing new in the attempt to correlate clinical observations with pathologic findings; in fact, this represents the fundamental purpose of the study of Pathology.

On first opening the book one is confronted with a gaudy unnatural frontispiece and is further discouraged by the inexact and muddled manner of considering the fundamental processes of inflammation and degeneration. It is hoped that the misquotation of Menken's term "Leucotaxine" as leucotoxine is a typographical error. The use of the term tubercular for tuberculous may be excusable in lay usage but appears as a glaring mistake in a medical textbook.

The short chapter on etiology of disease and the host reactions is poorly expressed confusing and too dogmatic. The one page on anaphylaxis confuses rather than elucidates the subject.

The greater portion of the book is devoted to special pathology. The consideration of pathologic processes by systems is more or less conventional. The evaluation of space in regard to subject matter is not in ratio to relative importance. There is an entire chapter of 70 pages on diseases of the cutaneous system with 12 of these devoted to leprosy, while all the diseases of the osseous system are contained in less than 10 pages.

In the important subject of neoplasia there is little attempt at clinical correlation.

The illustrations are plentiful but of mediocre quality. With the present photographic methods there seems little excuse for the drawings, many of which convey little information. A number of the photomicrographs are not representative of the condition; for instance, figure 274, adenoma, appears to be an endometrial hyperplasia; figure 290, carcinoma of the breast (intraductal) shows no clear evidence of malignancy in the field represented. Such inaccuracies seriously threaten the value of the book.

The references are restricted to publications in English and this fault is further emphasized by the fact that they are for the most part outdated.

The concluding chapter on the autopsy may serve as an outline for the student in the preparation of a protocol.

On the whole this book is disappointing.

C. G. W.

*The Care of a Small Rat Colony.* By ROLLAND J. MAIN, Ph.D. 101 pages; 22 × 14.5 cm. C. V. Mosby Co., St. Louis. 1939. Price, \$2.00.

With due emphasis on practical problems Dr. Main tells his experiences with a colony of 750 rats maintained on a restricted budget. He treats such questions as type of rat, equipment, care, and costs, with notes on the making of records and breeding routine. Considerable space is given to the mixing of feed, a necessary procedure when foods are to be tested and one that reduced the cost of dry food to 53 cents per adult rat per year.

As the apologia intimates, however, this book will not completely fill the needs of the average worker since it deals almost exclusively with the requirements of the author's laboratory. A procedure for vitamin D assay is given in detail. The inclusion of more data on fertility and mortality would have made the book more useful though somewhat less readable.

This book adequately describes the fundamental care necessary for raising a standard experimental rat.

E. G. B.

## COLLEGE NEWS NOTES

### GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged:

#### *Books*

Dr. William David Sansum, F.A.C.P., and Dr. Alfred E. Koehler (Associate), both of Santa Barbara, Calif., "A Manual for Diabetic Patients."

#### *Reprints*

Dr. Stanton T. Allison (Associate), New York, N. Y.—1 reprint;  
Col. Alexander T. Cooper, F.A.C.P. (MC), U. S. Army—1 reprint;  
Dr. Robert H. Felix (Associate), Lexington, Ky.—1 reprint;  
Dr. George Ginsberg (Associate), Hoboken, N. J.—1 reprint;  
Dr. A. Allen Goldbloom, F.A.C.P., New York, N. Y.—3 reprints;  
Dr. Harold I. Gosline (Associate), Ossining, N. Y.—19 reprints, 1 translation and 1 bulletin;  
Dr. Augustus A. Hall, F.A.C.P., Columbus, Ohio—3 reprints;  
Dr. Arthur O. Hecker (Associate), Woodville, Pa.—1 reprint;  
Dr. Charles S. Higley, F.A.C.P., Cleveland, Ohio—1 reprint;  
Dr. Edward Sandling King, F.A.C.P., Wake Forest, N.C.—1 reprint;  
Dr. Rudolph Leiser (Associate), Eloise, Mich.—1 reprint;  
Dr. C. Ray Lounsberry, F.A.C.P., San Diego, Calif.—1 reprint;  
Dr. Ralph Waldo Mendelson, F.A.C.P., Albuquerque, N. M.—1 reprint;  
Dr. Michael A. Ogden, F.A.C.P., New Orleans, La.—4 reprints;  
Dr. Richard E. Olsen, F.A.C.P., Pontiac, Mich.—5 reprints;  
Dr. William K. Purks, F.A.C.P., Vicksburg, Miss.—1 reprint;  
Dr. Harold L. Rakov (Associate), Kingston, N. Y.—1 reprint;  
Dr. Alexander F. Robertson, Jr., F.A.C.P., Staunton, Va.—1 reprint;  
Dr. Rafael Rodriguez-Molina, F.A.C.P., San Juan, P. R.—1 reprint;  
Dr. Albert Soiland, F.A.C.P., Los Angeles, Calif.—7 reprints;  
Dr. Leon J. Solway, F.A.C.P., Toronto, Ont., Canada—2 reprints;  
Dr. Frederick R. Taylor, F.A.C.P., Hight Point, N. C.—1 reprint;  
Dr. Myer Teitelbaum (Associate), Detroit, Mich.—1 reprint;  
Dr. Morris M. Weiss, F.A.C.P., Louisville, Ky.—3 reprints;  
Dr. Edward E. Woldman (Associate), Cleveland, Ohio—1 reprint;  
Dr. Bernard L. Wyatt, F.A.C.P., Tucson, Ariz.—1 reprint.

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### 1940 PROGRAM OF POSTGRADUATE COURSES

The American College of Physicians' Committee on Postgraduate Education and the Board of Regents announce the following special limited Postgraduate Courses, to be given preceding the 24th Annual Session of the College in Cleveland, April 1-5, 1940:

#### *Ann Arbor, Mich.*

No. 1—General Medicine—University of Michigan, Dr. Cyrus C. Sturgis, Director; March 18-30.

*Detroit, Mich.*

No. 2—Medicine in Industry—Henry Ford Hospital; Dr. Frank Sladen, Director; March 25–30.

*New York City*

No. 3—Allergy—Cornell University Medical College; Dr. Robert A. Cooke, Director; March 18–30.

*Columbus, Ohio*

No. 4—Hematology—Ohio State University; Dr. Charles A. Doan, Director; March 25–30.

*Iowa City, Iowa*

No. 5—Circulatory Diseases—State University of Iowa; Dr. Fred M. Smith, Director; March 25–30.

This is the third year of this activity by the College. The College has been able to make these courses available to its Fellows and Associates at minimum cost, because the College itself assumes full responsibility for promotion, advertising, printing and registration, as its contribution to its members.

The registration fee for each two-weeks course will be \$40; for each one-week course, \$20. One-half of the registration fee will be payable at time of registration and the balance shall be paid not later than March 12, a week in advance of the opening of the courses. The advance payment may be refunded by the College to any registrant who, for adequate reason, is unable to pursue the course, provided notice of withdrawal is registered ten days in advance of the opening of the courses.

Full description of the courses and other announcements appear in a special Bulletin, distributed to members. The number of admissions to each course will necessarily be restricted according to facilities. Registrations will be assigned in order of receipt.

The College will record all registrations with the respective institutions offering courses and will directly reimburse those institutions for each student-physician at the specified registration fee. A Matriculation Card will be sent each registrant from the College office when the fee has been paid in full.

## EDUCATIONAL FILMS

It has been suggested by some members of the College that as a part of its program of aid to postgraduate medicine the College might well interest itself in the possible extension of the utilization of educational medical films dealing with various aspects of internal medicine. To assist the College in collecting data on the number of such films now in use, all our members are asked to forward to the President, Dr. O. H. Perry Pepper, at 4200 Pine St., Philadelphia, any and all information they may possess concerning such films, including their subject matter and the address of their owners.

## REGIONAL MEETING OF KENTUCKY MEMBERS

A regional meeting of Fellows and Associates of the American College of Physicians residing in Kentucky was held at Louisville, December 14, 1939, under the Governorship of Dr. Chauncey W. Dowden. The afternoon was devoted to the following program at the Louisville City Hospital:

1. Staphylococcemia Cured with Sulphapyridine (with report of a case). Dr. Frank M. Stites, F.A.C.P.

2. Some Observations on Diphtheria Immunizations in Louisville. Dr. Hugh R. Leavell, F.A.C.P.
3. Banti's Syndrome Due to Hodgkin's Disease. Dr. Harold Gordon, F.A.C.P.
4. Case Presentation. Dr. Harry S. Frazier, F.A.C.P.
5. Clinico-Pathological Conference. Drs. John Walker Moore, F.A.C.P. and Aura J. Miller, F.A.C.P.
6. Prostigmin in Myasthenia Gravis. Dr. J. J. Moren, F.A.C.P.

Dr. Sam A. Overstreet, F.A.C.P., was in charge of arrangements.

In the evening a Dinner was held at the Pendennis Club in honor of Dr. O. H. Perry Pepper, President of the College, who delivered an address.

Out of an active membership of about 54 members in Kentucky, 50 were present at the scientific meeting and at the dinner. Every member of the College from Louisville was in attendance. It was generally agreed that this was the most successful regional meeting the Kentucky members have yet conducted. For 1940 the Kentucky Meeting will be held at Lexington.

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#### REGIONAL MEETING OF KANSAS MEMBERS

A regional meeting of the Fellows and Associates of the College residing in Kansas was held at Wichita, November 18, 1939, under the Governorship of Dr. Thomas T. Holt. An all-day session was held, starting at 10:30 in the morning and continuing after dinner in the evening. The program was as follows:

- 10:30 a.m. Pathological Conference, St. Francis Hospital. Dr. C. A. Hellwig, Wichita, Kansas.
- 1:00 p.m. "The Histamine Test in Arterial Hypertension." Dr. Maurice Snyder, Salina, Kansas.
- "A New Therapeutic Agent in the Treatment of Diarrhea." Dr. Harold H. Jones, F.A.C.P., Winfield, Kansas.
- "Physiology, Relative to the Kidney." Dr. Earl L. Mills (Associate), Wichita, Kansas.
- "An Investigation of Important Factors Bearing upon the Specificity and Interpretation of Serological Tests Used in the Diagnosis of Syphilis." Dr. N. P. Sherwood, Professor of Bacteriology, Lawrence, Kansas.
- "Electroencephalography." Dr. Norman Reider (Associate), Topeka, Kansas.
- "Lymphosarcoma of the Epidural Space." Dr. Ralph L. Drake (Associate), Wichita, Kansas.
- "Report on Results of Treatment with Metrazol." Dr. Ralph M. Fellows, F.A.C.P., Osawatomie, Kansas.
- "Insulin Therapy in Mental Diseases." Dr. D. V. Conwell, F.A.C.P., Halstead, Kansas.
- 6:30 p.m. Dinner.
- "Endocrines and Vitamines." Dr. J. S. Hughes, Professor of Biochemistry, Manhattan, Kansas.
- "What the Clinician Should Know About Edema." Dr. P. M. Krall (Associate), Kansas City, Kansas.

## PUERTO RICAN MEMBERS' MEETING

On the night of December 12 the members of the Puerto Rico Chapter of the American College of Physicians gave a Dinner in honor of Dr. Richard A. Kern, F.A.C.P., of the University of Pennsylvania, who was visiting Puerto Rico as a guest of honor of the Puerto Rico Medical Association, and who addressed the members of the Association on several occasions during the celebration of their annual scientific assembly. The following Fellows were present at the Dinner:

Dr. Ramón M. Suárez,  
Dr. O. Costa Mandry,  
Dr. Enrique Koppisch.

The following Associates were also present:

Dr. Antonio Ortiz,  
Dr. Luis Morales,  
Dr. Carlos Muñoz McCormick,  
Dr. M. de la Pila Iglesias,  
Dr. Juan Sabater,  
Dr. Francisco Landron.

At the meeting of the House of Delegates of the Puerto Rico Medical Association on December 9, Dr. O. Costa Mandry, F.A.C.P., was elected President of the Puerto Rico Medical Association for the year 1940.

Dr. Carl V. Weller, F.A.C.P., Professor of Pathology and Chairman of the Department of Pathology, University of Michigan Medical School, is serving as President of the American Association of Pathologists and Bacteriologists.

Dr. Ralph O. Clock, F.A.C.P., Scarsdale, N. Y., was the author of six articles published in Surgery, Gynecology and Obstetrics during the years 1933 to 1938, embodying the results of his research studies on the sterility of surgical catgut sutures. Dr. Clock emphasized the need of adequate control of suture sterility in the United States and advocated that the Food and Drug Administration of the United States Department of Agriculture set up the necessary equipment and personnel for conducting the work of testing the sterility of catgut sutures in an impartial manner. Beginning January 1, 1940, the bacteriological test proposed by Dr. Clock became official through its adoption in the United States Pharmacopoeia as a standard, under the title, "Tests for the Sterility of Solids."

The Dallas Academy of Internal Medicine was recently organized and Dr. D. W. Carter, Jr., F.A.C.P., elected President. The first meeting of the Academy was held recently, addressed by Dr. George Herrmann, F.A.C.P., Professor of Medicine at the University of Texas, as the guest speaker. Among members of the new Academy appeared the names of the following College Fellows, all of Dallas:

Dr. R. W. Baird, Dr. R. M. Barton, Dr. C. Frank Brown, Dr. D. W. Carter, Jr., Dr. C. M. Grigsby, Dr. R. B. McBride, Dr. W. H. Potts, Jr., Dr. W. G. Reddick, Dr. Sam Shelburne, Dr. R. M. Smith, Dr. J. S. Sweeney, Dr. George Underwood, Dr. H. M. Winans.

The following Associates are also listed in the membership:

Dr. E. P. Leeper, Dr. M. Hill Metz, Dr. M. B. Whitten.

The California Sanatorium Association held its Annual Meeting at the Wish-I-Ah Sanatorium, Fresno County, on November 11, 1939, under the Presidency of Dr. Harold Guyon Trimble, F.A.C.P., of Oakland. Among speakers on the program were:

Dr. Chesley Bush, F.A.C.P., Livermore, "Report on American Trudeau Society reorganization"; Dr. E. P. Smart, Associate, "What should be the details of contagious technic used on a tuberculosis ward by the attending nurses"; Dr. Charles L. Ianne, F.A.C.P., San Jose, "Is the presence of a negative tuberculin reaction desirable in employees who are going to work on tuberculosis wards"; Dr. F. M. Pottinger, Sr., F.A.C.P., Monrovia, "Therapeutic Use of Tuberculin."

Dr. R. M. Lymburner, F.A.C.P., Hamilton, Ontario, Canada, addressed the Grey County Medical Society, at Owen Sound, Ontario, November 8, on "Heart Failure and Its Therapeutic Management"; on November 22, Dr. Lymburner addressed the Huron County Medical Society at Seaforth, Ontario, on "Principles and Treatment of Congestive Heart Failure."

Dr. Richard M. Burke (Associate), Clinton, Okla., has been appointed Superintendent of the Western Oklahoma Tuberculosis Sanatorium.

Dr. Edwin Chester Swift, F.A.C.P., Jacksonville, Fla., was elected 1st Vice President, and Dr. Arthur Jones Logie (Associate), Jacksonville, Fla., was elected 2nd Vice President of the Florida East Coast Medical Association at its Twelfth Annual Meeting held at Ponte Vedra, Fla., on November 10-11, 1939.

Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J., spoke on November 20, 1939, on "Recent Trends in the Treatment of Coronary Heart Disease" at the Fourth Annual Series of Louis Adler Lectures on Cardiology, sponsored by the Medical Board of the Manhattan General Hospital.

Dr. Morris M. Weiss, F.A.C.P., Louisville, Ky., addressed the Fourth Annual Meeting of the Gulf Coast Clinical Society in Mobile, Ala., on October 27, 1939, on "The Treatment of Coronary Disease."

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., spoke on "Inhalant Allergy: Recent Experiences" at a meeting of the Kings County Medical Society and the Academy of Medicine of Brooklyn, at Brooklyn, N. Y., on December 19, 1939.

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md., spoke at a combined meeting of the Bradford County and Tioga County Medical Societies held at Troy, Pa., November 28, 1939, on "Diagnosis of Operable Chest Conditions."

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, Pa., conducted the Fifth Seminar of 1939 before the Lycoming County Medical Society, Williamsport, Pa., November 24, 1939, on "Vitamins and Food Values in Health and Disease."

Dr. Carlos E. Fallon (Associate), Newburgh, N. Y., was appointed assistant attending physician in the Gastroenterology Department of the New York University College of Medicine Clinic on December 12, 1939.

The Council of the New York Academy of Medicine plans to hold their Thirteenth Graduate Fortnight, October 14-25, 1940.

Under the Presidency of Dr. Louis H. Bauer, F.A.C.P., Hempstead, N.Y., the Second District Branch of the Medical Society of the State of New York held its 33rd Annual Meeting, November 16, 1939. Among those to present symposia were the following:

Dr. Henry M. Moses, F.A.C.P., Brooklyn, N. Y., "Neoplasms of the Chest";  
Dr. Carl H. Greene, F.A.C.P., Brooklyn, N. Y., "Differential Diagnosis Between Lung Tumors and Chronic Inflammatory Disease of the Lungs";

Dr. Foster Murray, F.A.C.P., Hempstead, N. Y., "Early Clinical Diagnosis";  
Dr. Willard J. Davies, F.A.C.P., Rockville Centre, N. Y., "Correlation of Roentgen Ray with Clinical Findings";

Drs. James C. Walsh, F.A.C.P., Farmingdale, N. Y., and Edwin P. Kolb, F.A.C.P., Holtsville, N. Y., "Medical Management Including Sanatorium Care."

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The University of North Carolina opened a new building for The School of Medicine and The Division of Public Health at Chapel Hill, N. C., Monday, December 4, 1939. Among those who participated in the opening exercises were:

Dr. William deB. MacNider, F.A.C.P.

Dr. I. H. Manning, F.A.C.P.

Dr. C. C. Carpenter, F.A.C.P., Wake Forest, N. C.

Dr. W. C. Davison, F.A.C.P., Durham, N. C.

An address on "The Making of a Clinician" was given by Dr. David Riesman, F.A.C.P., Philadelphia, Pa., and an address on "The Old Medical School of the University—Dr. Richard Henry Whitehead, Dr. Charles Staples Mangum" was given by Dr. James K. Hall (Associate), Richmond, Va.

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Dr. George Ginsberg (Associate), Hoboken, N. J., read a paper entitled "Results with the Prolonged Use of Protamine Zinc Insulin in the Treatment of Diabetes Mellitus," at the Second Fall Clinical Conference of the Medical Society of New Jersey, held at Jersey City, N. J., November 9-10, 1939.

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The New Jersey Gastro-Enterological Society, at its Annual Meeting, December 4, 1939, in Newark, N. J., elected Dr. Manfred Kraemer, F.A.C.P., Newark, President, and Dr. Hyman I. Goldstein (Associate), Camden, Vice President.

---

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, was one of four to whom the first award of the National Canners Association was made on November 20, 1939, "for signal service to the canning industry and to the public health in the discovery of methods leading to the prevention of botulism and in the development of the canning technic relative thereto."

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Dr. Leslie M. Smith, F.A.C.P., El Paso, Texas, who is now President of the Texas Dermatological Society, recently took office as President of the El Paso County Medical Society for the year 1940.

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Dr. Eugene M. Landis, F.A.C.P., University, Va., spoke at a recent meeting of the University of Virginia Medical Society on "Kidney Extracts and Hypertension." Later, Dr. Landis spoke at the 24th Postgraduate Clinic, sponsored by the

University Medical School, on "Pathological Physiology of Human Hypertension" and at the Roanoke Academy of Medicine on "Hypertension."

---

Colonel J. E. Ash, F.A.C.P., Curator, Army Medical Museum, Washington, D. C., was one of the guest speakers at the meeting of the Southeastern Branch Society of the American Urological Association at Biloxi, Miss., December 8-9.

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Dr. Russell H. Oppenheimer, F.A.C.P., Emory University, who was formerly the College Governor for the State of Georgia, was recently installed as President of the Association of American Medical Colleges.

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Among the guest speakers at the Third Annual Session of the Atlanta Graduate Medical Assembly were Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich.; Dr. Wm. E. Chamberlain, F.A.C.P., Philadelphia, Pa.; and Dr. Philip S. Hench, F.A.C.P., Rochester, Minn.

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Dr. M. E. Winchester, F.A.C.P., Brunswick, Ga., spoke on "Special Administrative Problems of the County Health Officer" at a recent meeting of the International Society of Medical Health Officers, held in Pittsburgh, Pa.

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Dr. Charles W. Dunn (Associate), Philadelphia, Pa., led a round-table discussion on "Endocrine Problems of Childhood" at the annual meeting of the Virginia Pediatric Society.

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Among the speakers at a joint meeting of the Neuropsychiatric Society of Virginia and the North Carolina Neuropsychiatric Association were the following:

- Dr. David C. Wilson, F.A.C.P., University, Va.—"The Present Status of Our Understanding of Convulsive Disorders";
  - Dr. R. Finley Gayle, Jr., F.A.C.P., Richmond, Va.—"The Treatment of Parkinsonism with a Preparation of Belladonna Root";
  - Dr. J. K. Hall (Associate), Richmond, Va.—"The Language-Barrier in Depressed States."
- 

Dr. William B. Porter, F.A.C.P., Richmond, Va., has been elected President of the American Clinical and Climatological Association.

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Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., has been awarded the 1939 Gold Medal for distinguished medical achievements, by the Phi Lambda Kappa Fraternity, at their Convention, held at Park Central Hotel, New York, on January 1, 1940.

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Dr. Wingate M. Johnson, F.A.C.P., Winston-Salem, N. C., has been appointed Editor of the recently established North Carolina State Medical Journal.

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Dr. E. A. Hines, F.A.C.P., Seneca, S. C., was reelected President of the Piedmont Postgraduate Clinical Assembly and Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., who is the College Governor for this state, was elected a Vice-President.

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Dr. Conley H. Sanford, F.A.C.P., Memphis, Tenn., has been recently made Professor and Head of the Department of Medicine of the University of Tennessee Col-

lege of Medicine to succeed Dr. James B. McElroy, F.A.C.P., who resigned because of ill health.

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Dr. Ernest Kelley, F.A.C.P., Omaha, Nebr., has been appointed Head of the Department of Nervous and Mental Diseases at the Creighton University School of Medicine.

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Dr. David P. Barr, F.A.C.P., St. Louis, Mo., gave an address at the Cornell University Medical College December 13 on "The Nature of Obesity."

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The following Fellows of the College participated in the program of scientific lectures sponsored by the College of Physicians of Philadelphia:

Dr. O. H. Perry Pepper (President, A.C.P.), Philadelphia, Pa.—"Medical Problems of Advancing Age";

Dr. Howard T. Karsner, Cleveland, Ohio—"Certain Ovarian Tumors Associated with Sexual Endocrine Dysfunction."

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Dr. Joseph McFarland, Philadelphia, Pa., will give a lecture on "The Pathological Diagnosis of Cancer in Man" on April 3, and Dr. William Edward Chamberlain, Philadelphia, Pa., will give a lecture on "The X-Ray as an Aid in Diagnosis" on April 12.

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Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, who is Vice President of the Section on Medical Sciences of the American Association for the Advancement of Science, delivered an address on "The Physiology of Coronary Blood Flow" at their meeting in Columbus, Ohio, December 27-30.

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Dr. Irving Wright was the guest lecturer of the Chicago Medical Society on December 20. The subject was "Arteriosclerosis Obliterans; Its Modern Conception of Its Social Significance, Diagnosis and Treatment."

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Among physicians taking part in the instruction in the Illinois State Medical Society's Postgraduate Conference at Champaign, Ill., December 7, were:

Dr. Francis E. Senear, F.A.C.P., Chicago—"The Treatment of Athlete's Foot and Other Fungus Infections of the Skin."

Dr. Robert A. Black, F.A.C.P., Chicago—"The Treatment of Common Ailments in Children."

Dr. James H. Hutton, F.A.C.P., Chicago—"The Management of the Male and Female Climacteric."

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Dr. Nathan B. Van Etten, F.A.C.P., New York City, President-Elect of the American Medical Association, delivered an address on "An American Health Program" at the sesquicentennial celebration of the Medical Society of South Carolina at Charleston on December 5.

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Dr. William S. McCann, F.A.C.P., Rochester, N. Y., addressed the Kansas City (Mo.) Academy of Medicine, December 15, on "Modern Trends in the Study of Kidney Disease."

Dr. William W. Graves, F.A.C.P., Professor and Director of the Department of Neuropsychiatry, St. Louis University School of Medicine, was recently honored by the St. Louis Medical Society with a certificate of merit and a gold medal. The award was made in recognition of work by Dr. Graves which "resulted in new approaches to the qualitative evaluation of inherited variations in relation to the inherited qualities of human constitution, expressed in inherited predisposition to health or disease, and in inherited capacity for education, for adaptability and for longevity."

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Dr. Warfield T. Longcope, F.A.C.P., Baltimore, was recently elected President of the Board of Scientific Directors of the Rockefeller Institute for Medical Research.

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Among speakers at the Sixth Conference of Southern Pathologists, held at Memphis, November 20, were:

Dr. William R. Mathews, F.A.C.P., Shreveport—"The Aspiration Biopsy."

Dr. Charles W. Duval, F.A.C.P., New Orleans—"Teaching of Pathology and Bacteriology as One Subject Matter."

Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C.—"The Present Day Status of Clinical Pathology and Problems of the Clinical Pathologist."

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Under the Presidency of Dr. Raymond G. Taylor, F.A.C.P., Los Angeles, the Radiological Society of North America held its annual meeting at Atlanta, December 11-15, 1939. The program was divided among refresher courses for two hours each morning, general sessions the balance of the morning and sessions for diagnostic and therapeutic subjects in the afternoons.

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Dr. Frederick T. Lord, F.A.C.P., Clinical Professor of Medicine Emeritus of Harvard Medical School, Boston, delivered the fifth annual John W. Bell Tuberculosis Lecture before the Hennepin County Medical Society at Minneapolis on December 4, his subject being "The Clinical Aspects and Diagnosis of Pulmonary Lesions."

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Dr. W. Laurence Whittemore, F.A.C.P., and Dr. James R. Lisa, F.A.C.P., both of New York City, are members of a committee in charge of work at the City Hospital on Welfare Island in connection with a newly installed special chamber for experiments in crymotherapy, or the "frozen sleep" method of treating cancer.

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Lt. Col. William D. Fleming, F.A.C.P., M.C., U.S. Army, Edgewood Arsenal, Md., addressed the Philadelphia County Medical Society, November 27, on "Medical Aspects of Chemical Warfare."

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Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, has been elected President of the Central Society for Clinical Research.

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Dr. Thomas T. Mackie, F.A.C.P., New York City, has been made President-Elect of the American Society of Tropical Medicine.

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Dr. William C. Menninger, F.A.C.P., Topeka, Kan., has been elected Secretary-Treasurer of the Central Neuropsychiatric Association.

## NEW ELECTIONS TO COLLEGE MEMBERSHIP

At a meeting of the Board of Regents December 17, 1939, at the headquarters building, Philadelphia, the following candidates were regularly elected to the class indicated:

## ELECTIONS TO FELLOWSHIP

December 17, 1939

*Fellowship Candidates**Sponsors*

## ALABAMA

Seale Harris, Jr., Birmingham  
William Lindsay Miller, Gadsden

John B. Youmans, Groesbeck Walsh, Fred Wilkerson  
J. Harold Watkins, Seale Harris, Fred Wilkerson

## CALIFORNIA

Richard Donald Evans, Los Angeles  
Donald E. Griggs, Los Angeles  
Eberle Kost Shelton, Los Angeles  
Elliott Plummer Smart, Murphys  
Edward Kupka, Olive View  
Walter Cyril Nalty, San Fernando  
Albert Howell Elliot, Jr., Santa Barbara  
Russell Lowell Sands, Santa Monica

B. O. Raulston, Arthur Stanley Granger, James F. Churchill  
R. Manning Clarke, Percy T. Magan, James F. Churchill  
Fred B. Clarke, F. M. Pottenger, James F. Churchill  
E. W. Hayes, Sidney J. Shipman, Ernest H. Falconer  
F. M. Pottenger, Carl R. Howson, James F. Churchill  
Charles M. Griffith, Bryan M. Riley, James F. Churchill  
Hilmar O. Koefod, Harry E. Henderson, James F. Churchill  
Roland Cummings, S. M. Alter, James F. Churchill

## CONNECTICUT

Ralph Lawrence Gilman, Storrs

G. Gardiner Russell, Otto G. Wiedman, Francis G. Blake, Charles H. Turkington

## DISTRICT OF COLUMBIA

John A. Reisinger, Washington  
Robert Lomax Wells, Washington

John Minor, Thomas S. Lee, Wallace M. Yater  
W. Cabell Moore, Henry C. Macatee, Wallace M. Yater

## MEDICAL CORPS, U. S. ARMY

James Carre Magee, Washington, D. C.  
Frank Wiley Wilson, Fort Benning, Ga.

William L. Sheep, Joseph R. Darnall, Wallace M. Yater  
C. R. Reynolds

## FLORIDA

John Webster Merritt, Jacksonville

R. H. McGinnis, Louie Limbaugh, T. Z. Cason

## GEORGIA

Mark Stovall Dougherty, Jr., Atlanta  
William Rudy Minnich, Atlanta  
Thomas Fort Sellers, Atlanta  
William Hugh Trimble, Atlanta  
James Fletcher Hanson, Macon  
Thomas Llewellyn Ross, Jr., Macon

Allen H. Bunce, Russell H. Oppenheimer, Glenville Giddings  
H. C. Sauls, Carter Smith, Glenville Giddings  
Guy G. Lunsford, Joe P. Bowdoin, Glenville Giddings  
Hal M. Davison, Trimble Johnson, Glenville Giddings  
Alvin E. Siegel, J. D. Applewhite, Glenville Giddings  
T. E. Rogers, Stewart R. Roberts, Glenville Giddings

*Fellowship Candidates*

William Pickens Harbin, Jr., Rome

Charles Henry Sprague, Boise

Thomas Austin Starkey, Beardstown

M. Herbert Barker, Chicago

John Harold Mills, Chicago

Walter Lincoln Palmer, Chicago

Eugene Solomon Talbot, Chicago

Michael Zeller, Chicago

Richard Hale Young, Evanston

Harry Willard Shuman, Rock Island

Villairs Thomas Austin, Urbana

Charles Hilbert Drenckhahn, Urbana

Noble Pierce Sherwood, Lawrence

Arthur Joseph Revell, Pittsburg

James Graves Stewart, Topeka

Marion Foree Beard, Louisville

Archibald Donaldson Kennedy, Louisville

Frank Anthony Simon, Louisville

Woodford Bates Troutman, Louisville

Grace Arabell Goldsmith, New Orleans

Stanley George Wolfe, Shreveport

Donald Howard Daniels, Portland  
Richard Sylvester Hawkes, Portland

Alan Bernstein, Baltimore

Ernest Samuel Cross, Baltimore

Francis Wilcox Gluck, Baltimore

*Sponsors*Trimble Johnson, Joseph Yampolsky, Glenville  
Giddings

## IDAHO

Harry A. Collins, Edward W. Anderson, Tom  
B. Throckmorton

## ILLINOIS

F. G. Norbury, Harold Swanberg, Samuel E.  
MunsonLowell D. Snorf, N. S. Davis, III, James G.  
CarrJosiah J. Moore, Frederick O. Fredrickson,  
James G. CarrLaurence E. Hines, N. S. Davis, III, James G.  
CarrJ. Roscoe Miller, Arthur E. Mahle, James G.  
CarrWilliam H. Welker, Leon Unger, James G.  
CarrJ. Roscoe Miller, Arthur E. Mahle, James G.  
CarrHugh A. Beam, C. D. Mercer, Samuel E. Mun-  
sonE. M. Stevenson, Gerald M. Cline, Samuel E.  
MunsonE. M. Stevenson, Gerald M. Cline, Samuel E.  
Munson

## KANSAS

Henry N. Tihen, Fred J. McEwen, Thomas  
T. HoltWilliam C. Menninger, Ralph M. Fellows,  
Thomas T. HoltWilliam C. Menninger, Philip W. Morgan,  
Thomas T. Holt

## KENTUCKY

J. Murray Kinsman, J. Richard Gott, Jr., C. W.  
DowdenH. V. Noland, J. Murray Kinsman, C. W.  
DowdenJ. Murray Kinsman, Sam A. Overstreet, C. W.  
DowdenVirgil E. Simpson, Arthur Clayton McCarty,  
C. W. Dowden

## LOUISIANA

John H. Musser, Philip H. Jones, J. E.  
KnightonClarence H. Webb, M. D. Hargrove, J. E.  
Knighton

## MAINE

E. W. Gehring, E. R. Blaisdell, E. H. Drake  
Harry S. Emery, E. R. Blaisdell, E. H. Drake

## MARYLAND

Louis P. Hamburger, Thomas P. Sprunt, Henry  
M. Thomas, Jr.Thomas P. Sprunt, Louis Hamman, Henry M.  
Thomas, Jr.Walter A. Baetjer, Sydney R. Miller, Henry  
M. Thomas, Jr.

*Fellowship Candidates*

Lewis Perkins Gundry, Baltimore  
 Harold Raymond Peters, Baltimore  
 David Tenner, Baltimore  
 Samuel Whitehouse, Baltimore  
 Perry Franklin Prather, Hagerstown

*Sponsors*

T. Nelson Carey, William S. Love, Jr., Henry M. Thomas, Jr.  
 Thomas P. Sprunt, Harvey G. Beck, Henry M. Thomas, Jr.  
 William S. Love, Jr., J. Sheldon Eastland, Henry M. Thomas, Jr.  
 Paul W. Clough, Thomas P. Sprunt, Henry M. Thomas, Jr.  
 Victor F. Cullen, R. S. Stauffer, Henry M. Thomas, Jr.

## MASSACHUSETTS

Earle MacArthur Chapman, Boston  
 Greene Smith FitzHugh, Boston  
 James Carlin McAdams, Fall River

F. Dennette Adams, B. H. Ragle, William B. Breed  
 Maurice Fremont-Smith, Robert S. Palmer, William B. Breed  
 William Mason, Charles C. Wolferth, William B. Breed

## MICHIGAN

Herman Marvin Pollard, Ann Arbor  
 Louis John Bailey, Detroit  
 Nicola Gigante, Detroit  
 John Doyle Littig, Kalamazoo  
 Richard Ellsworth Olsen, Pontiac

Arthur C. Curtis, Herman H. Riecker, Henry R. Carstens  
 Richard Campbell Connelly, Robert Conrad Moehlig, Henry R. Carstens  
 P. L. Ledwidge, Edward D. Spalding, Henry R. Carstens  
 Arthur C. Curtis, Cyrus C. Sturgis, Henry R. Carstens  
 Harold R. Roehm, George A. Sherman, Henry R. Carstens

## MINNESOTA

Charles Everard Lyght, Northfield

J. A. Myers, Elmer L. Sevringhaus, E. V. Allen

## MISSOURI

Sim Fields Beam, St. Louis  
 Kenneth Franklin Glaze, St. Louis  
 Harold Gould Newman, St. Louis

Walter Baumgarten, Anthony B. Day, A. C. Griffith  
 Walter Baumgarten, Charles Hugh Neilson, A. C. Griffith  
 Howard A. Rusk, Walter Baumgarten, A. C. Griffith

## MONTANA

Malcolm Duncan Winter, Miles City

Allen R. Foss, John Paul Ritchey, Louis H. Fligman (deceased)

## NEBRASKA

Chester Quay Thompson, Omaha

Rodney W. Bliss, Lynn T. Hall, Warren Thompson

## NEW JERSEY

Thomas Krapfel Lewis, Camden  
 Jerome George Kaufman, Newark  
 Sigurd Walter Johnsen, Passaic

Ralph K. Hollinshed, Hilton S. Read, George H. Lathrope  
 Aaron E. Parsonnet, Edgar Mayer, George H. Lathrope  
 Manfred Kraemer, George Milton Knowles, George H. Lathrope

*Fellowship Candidates**Sponsors*

## NEW YORK

George William Weber, Albany  
 James Arthur Buchanan, Brooklyn  
 George B. Dorff, Brooklyn  
 Stuart L. Vaughan, Buffalo  
 Cornelius Packard Rhoads, New York  
 Ralph Horton, Oneonta  
 James Murray Flynn, Rochester  
 Clement Joseph Handron, Troy  
 Alson Joye Hull, Troy  
 Clarence Orion Cheney, White Plains

F. W. Holcomb, James F. Rooney, C. F. Tenney  
 George Forbes, Philip I. Nash, C. F. Tenney  
 Irving J. Sands, Harry R. Litchfield, C. F. Tenney  
 A. H. Aaron, Clayton W. Greene, Nelson G. Russell  
 Thomas T. Mackie, James Alex. Miller, C. F. Tenney  
 J. K. Deegan, J. Burns Amberson, Jr., C. F. Tenney  
 John M. Swan, C. Clyde Sutter, Nelson G. Russell  
 Crawford R. Green, James F. Rooney, C. F. Tenney  
 Crawford R. Green, Stephen H. Curtis, C. F. Tenney  
 Charles A. McKendree, Willard C. Rappleye, C. F. Tenney

## NORTH CAROLINA

Walter Reece Berryhill, Chapel Hill  
 Thomas Williams Baker, Charlotte  
 Sidney Ferring LeBauer, Greensboro  
 Erle Bulla Craven, Jr., Lexington  
 George Erick Bell, Wilson

William de B. MacNider, Soma Weiss, Charles H. Cocke  
 Edward J. Wannamaker, T. Preston White, Charles H. Cocke  
 Frederick R. Taylor, D. Waldo Holt, Charles H. Cocke  
 William de B. MacNider, Frederick R. Taylor, Charles H. Cocke  
 Thurman D. Kitchin, C. C. Carpenter, Hubert B. Haywood, Charles H. Cocke

## NORTH DAKOTA

Arthur Conwell Fortney, Fargo

Robert B. Radl, Leonard H. Fredricks, Julius O. Arnson

## OHIO

Tom Douglas Spies, Cincinnati  
 Roy Wesley Scott, Cleveland  
 Joseph Treloar Wearn, Cleveland  
 Casimir Joseph Czarnecki, Toledo

James S. McLester, Fred Wilkerson, A. B. Brower  
 V. C. Rowland, Walter M. Simpson, A. B. Brower  
 Howard T. Karsner, J. M. Hayman, Jr., A. B. Brower  
 C. W. Waggoner, Frank C. Clifford, A. B. Brower

## OKLAHOMA

John Barnhart Morey, Ada  
 Elbert Henderson Shuller, McAlester  
 Frederic Griffin Dorwart, Muskogee  
 Coyne Herbert Campbell, Oklahoma City

Hugh Jeter, J. T. Martin, Lea A. Riely  
 Henry H. Turner, L. J. Moorman, Lea A. Riely  
 E. Rankin Denny, Russell C. Pigford, Lea A. Riely  
 Henry H. Turner, L. J. Moorman, Lea A. Riely

## PENNSYLVANIA

Willard Daniel Kline, Allentown  
 Richard Thomas Ellison, Philadelphia  
 Hugh McCauley Miller, Philadelphia  
 Merritt Henry Stiles, Philadelphia  
 John Harrington Willard, Philadelphia

Henry I. Klopp, Laurence C. Milstead, Edward L. Bortz  
 H. L. Bockus, Ralph Pemberton, Edward L. Bortz  
 David Riesman, H. L. Bockus, Edward L. Bortz  
 T. Grier Miller, Charles C. Wolferth, George Morris Piersol, Edward L. Bortz  
 H. L. Bockus, H. Leon Jameson, Edward L. Bortz

*Fellowship Candidates*

Albert Preston Knight, Sayre  
 Wilfred Derwood Langley, Sayre  
 Hyman Abraham Slesinger, Windber

*Sponsors*

Stanley D. Conklin, John M. Higgins, Edward  
 L. Bortz  
 Stanley D. Conklin, Charles H. DeWan, Ed-  
 ward L. Bortz  
 Horace B. Anderson, Elwood W. Stitzel, R. R.  
 Snowden

## RHODE ISLAND

Morgan Cutts, Providence

Elihu S. Wing, Charles F. Gormly, Alex. M.  
 Burgess

## SOUTH DAKOTA

Donald Luther Kegaries, Rapid City

Charles F. Morsman, Nelson W. Barker, John  
 L. Calene

## TENNESSEE

Edward Guy Campbell, Memphis  
 Henry Bragg Gotten, Memphis  
 Joseph Franklin Hamilton, Memphis

Conley H. Sanford, William Calvert Chaney,  
 J. O. Manier  
 Richard E. Ching, William Calvert Chaney,  
 J. O. Manier  
 Conley H. Sanford, William Calvert Chaney,  
 J. O. Manier

## TEXAS

Jesse Bedford Shelmire, Dallas  
 Leslie McKnight Smith, El Paso  
 Henry Napoleon Gemoets, Houston  
 David Robert Sacks, San Antonio

C. Frank Brown, D. W. Carter, Jr., M. D. Levy  
 Orville E. Egbert, James J. Gorman, M. D.  
 Levy  
 Alvis E. Greer, David Greer, M. D. Levy  
 Lee Rice, Herbert Hill, M. D. Levy

## VIRGINIA

Burbridge Scott Yancey, Harrisonburg

J. Edwin Wood, Jr., H. B. Mulholland, Walter  
 B. Martin

## WASHINGTON

Harry Joseph Friedman, Seattle  
 Edward David Hoedemaker, Seattle

Lester J. Palmer, G. A. Dowling, C. E. Watts  
 Edwin G. Bannick, George H. Anderson, C. E.  
 Watts

## WEST VIRGINIA

Pat Alexander Tuckwiller, Charleston  
 Frank Jackson Holroyd, Princeton

Martin Loxley Bonar, Walter E. Vest, Albert  
 H. Hoge  
 Walter E. Vest, C. A. Ray, Albert H. Hoge

## WISCONSIN

Benjamin Jaffee Birk, Milwaukee

Andrew I. Rosenberger, Oscar Lotz, Rock  
 Sleyster

## CANAL ZONE

Gilbert Miller Stevenson, Gamboa

C. D. Briscoe, T. G. Guardia, William M.  
 James

## TERRITORY OF HAWAII

Stewart Edward Doolittle, Honolulu  
 Richard Eugene DeMonbrun Kepner,  
 Honolulu

Hastings Howland Walker, Nils P. Larsen,  
 Harry L. Arnold  
 Hastings Howland Walker, A. G. Schnack,  
 Harry L. Arnold

*Fellowship Candidates**Sponsors*

## DOMINION OF CANADA

*British Columbia*

Harold Archibald Des Brisay, Vancouver G. F. Strong, George H. Anderson, C. E. Watts

*Nova Scotia*

John Wilfred MacIntosh, Halifax Gerald R. Burns, R. J. Collins, H. A. Farris

*Ontario*

Trenholm Lawrence Fisher, Ottawa Warren S. Lyman, D. Sclater Lewis, J. H. Holbrook

*Resolved*, that the following list of 9 be and herewith are elected to Fellowship in the American College of Physicians as of March 31, 1940:

## CONNECTICUT

Barnett Greenhouse, New Haven Benedict R. Harris, C. J. Bartlett, Francis G. Blake

## FLORIDA

Lucien Young Dyrenforth, Jacksonville R. H. McGinnis, William W. Kirk, T. Z. Cason

## GEORGIA

Harold Cook Atkinson, Macon T. E. Rogers, Stewart R. Roberts, Glenville Giddings

## MASSACHUSETTS

James Harvey Townsend, Boston Albert A. Hornor, G. Philip Grabfield, William B. Breed

## NEW YORK

Calvus Elton Richards, Clifton Springs Mark A. Brown, John H. Skavlem, Nelson G. Russell  
 Samuel S. Paley, New York Barnet P. Stivelman, Charles Walter Clarke, C. F. Tenney  
 Harold Inman Gosline, Ossining Myrtelle M. Canavan, Henry A. Christian, C. F. Tenney

## SOUTH CAROLINA

Lucius Emmett Madden, Columbia O. B. Mayer, J. Heyward Gibbes, Kenneth M. Lynch

## VIRGINIA

Andrew DeJarnette Hart, Jr., University J. Edwin Wood, Jr., H.B. Mulholland, Walter B. Martin

## ELECTIONS TO ASSOCIATESHIP

December 17, 1939

## ARIZONA

Leslie Rest Kobert, Phoenix Howell Randolph, Joseph Bank, Fred G. Holmes  
 Hilton John McKeown, Phoenix Robert S. Flinn, Orville Harry Brown, Fred G. Holmes  
 William Grant Ure, Tucson Cyrus C. Sturgis, Arthur C. Curtis, Fred G. Holmes

## CALIFORNIA

George Berdelle Hanson, Long Beach J. E. Walker, Fred B. Clarke, James F. Churchill

*Fellowship Candidates*

Roy Alexander Ouer, San Diego  
 Harold Chester Torbert, San Diego  
 Andrew Benton Stockton, San Francisco

*Sponsors*

William H. Barrow, Lyell C. Kinney, James F. Churchill  
 J. W. Sherrill, Arthur A. Marlow, James F. Churchill  
 Dwight L. Wilbur, Arthur L. Bloomfield, Ernest H. Falconer

## COLORADO

Clarke Horace Barnacle, Denver  
 Robert Todd Terry, Denver

Ward Darley, Jr., R. W. Arndt, James J. Waring  
 Ward Darley, Jr., C. S. Bluemel, James J. Waring

## CONNECTICUT

Edward Gipstein, New London  
 Carl Hendricks Wies, New London  
 Sidney Weinberg Jennes, Waterbury

Hugh B. Campbell, Cole B. Gibson, Charles H. Turkington  
 Arthur Bliss Dayton, George Blumer, Francis G. Blake, Charles H. Turkington  
 William E. Hill, John H. Foster, Charles H. Turkington

## DISTRICT OF COLUMBIA

Samuel Benjamin, Washington  
 Linn Fenimore Cooper, Washington  
 Harry Filmore Dowling, Washington  
 Joseph Francis Elward, Washington  
 Kenneth Francis Laughlin, Washington  
 Benjamin Manchester, Washington

J. Winthrop Peabody, William P. Argy, Wallace M. Yater  
 John Minor, Lewis C. Ecker, Wallace M. Yater  
 Walter K. Myers, Soma Weiss, Wallace M. Yater  
 Oscar B. Hunter, Isidore Lattman, Wallace M. Yater  
 Eugene R. Whitmore, Joseph L. Gilbert, Wallace M. Yater  
 Janvier W. Lindsay, E. Clarence Rice, Wallace M. Yater

## MEDICAL CORPS, U. S. NAVY

Joseph La Monte Zundell, Chelsea, Mass.

E. C. White, John M. McCants, Ross T. McIntire

## FLORIDA

Francis Dowdle Pierce, Fort Lauderdale  
 Samuel Marion Salley, Miami  
 David Wyest Exley, Miami Beach  
 Frazier James Payton, Miami Beach

Kenneth Phillips, P. B. Welch, T. Z. Cason  
 Warren W. Quillian, P. B. Welch, T. Z. Cason  
 Theodore J. Pfeffer, Frank S. Perkin, T. Z. Cason  
 William M. LeFevre, P. B. Welch, T. Z. Cason

## GEORGIA

Lawrence Easter Geeslin, Brunswick  
 John Richard Shannon Mays, Milledgeville

V. P. Sydenstricker, John B. Youmans, Glenville Giddings  
 George L. Echols, V. P. Sydenstricker, James E. Paullin, Glenville Giddings

## ILLINOIS

Richard Brooks Capps, Chicago  
 Angelo Samuel Geraci, Chicago  
 Donald Anton Hirsch, Chicago  
 Gilbert Henry Marquardt, Chicago  
 Eugene Lawrence Walsh, Chicago

J. Roscoe Miller, Laurence E. Hines, James G. Carr  
 Robert S. Berghoff, Italo F. Volini, James G. Carr  
 Robert S. Berghoff, Italo F. Volini, James G. Carr  
 J. Roscoe Miller, A. A. Goldsmith, James G. Carr  
 J. Roscoe Miller, Laurence E. Hines, James G. Carr

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George Clarence Turnbull, Evanston

Arthur Sterling Webb, Wheaton

Thomas Olney Dorrance, Bluffton

Arthur B. Richter, Flora

Brandt Ferguson Steele, Indianapolis

Lewis George Allen, Kansas City

Floyd Cornelius Taggart, Topeka

Robert Chester Lowe, New Orleans

Warde Baunton Allan, Baltimore

John Warner Parsons, Baltimore

Neil Louis Crone, Boston

Thomas Hale Ham, Boston

Wayne Clifton Barnes, Springfield

Kendall Bennett Holmes, Ann Arbor

John McFarland Sheldon, Ann Arbor

Jacob Myer Berris, Detroit

Harold Isadore Ginsberg, Detroit

Benjamin Juliar, Detroit

Mark Ronald McQuiggan, Detroit

Max Karl Newman, Detroit

Cleo Russel Gatley, Pontiac

Jacob Solomon Blumenthal, Minneapolis

George Frank Kowallis, Rochester

Edward Carl Rosenow, Jr., Rochester

Edward Virginius Swift, Rochester

*Sponsors*

Samuel J. Lang, Lowell D. Snorf, James G. Carr

Walter H. Watterson, Josiah J. Moore, James G. Carr

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Allen A. C. Nickel, Gustav L. Kaufmann, Robert M. Moore

Edgar F. Kiser, J. O. Ritchey, Robert M. Moore

J. O. Ritchey, Edgar F. Kiser, Robert M. Moore

## KANSAS

Fred E. Angle, Fred J. McEwen, Thomas T. Holt

William C. Menninger, Philip W. Morgan, Thomas T. Holt

## LOUISIANA

Edgar Hull, Louis A. Monte, J. E. Knighton

## MARYLAND

George W. Thorn, Thomas P. Sprunt, Henry M. Thomas, Jr.

Lav Martin, Thomas P. Sprunt, Henry M. Thomas, Jr.

## MASSACHUSETTS

J. H. Means, F. Dennette Adams, William B. Breed

George R. Minot, Chester S. Keefer, William B. Castle, William B. Breed

Theodore S. Bacon, Laurence D. Chapin, William B. Breed

## MICHIGAN

Cyrus C. Sturgis, Frank N. Wilson, Henry R. Carstens

Cyrus C. Sturgis, Arthur C. Curtis, Henry R. Carstens

George Barrie Hoops, Rollin H. Stevens, Henry R. Carstens

Harold A. Robinson, William H. Gordon, Henry R. Carstens

Robert J. Schneek, Harold J. Kullman, Henry R. Carstens

Harold J. Kullman, Samuel S. Altshuler, Henry R. Carstens

Saul Rosenzweig, William H. Gordon, Henry R. Carstens

Harold R. Roehm, George A. Sherman, Henry R. Carstens

## MINNESOTA

D. R. Hastings, S. A. Weisman, S. Marx White, E. V. Allen

Samuel F. Haines, E. J. Kepler, E. V. Allen

Philip W. Brown, J. A. Bargen, E. V. Allen

Henry W. Woltman, A. R. Barnes, E. L. Tuohy, E. V. Allen

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Frank I. Ridge, Sam H. Snider, A. C. Griffith

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James Edward Bovaird, Wolfeboro

Fred Ellsworth Clow, Wilmar M. Allen, Robert Brown Kerr

## NEW JERSEY

Frederick Hnat, Elizabeth

Horace R. Livengood, Michael Vinciguerra, George H. Lathrope

Joseph Alphonsus Smith, Metuchen

Louis F. Wetterberg, John V. Smith, George H. Lathrope

Harold Herbert Goldberg, Newark

Aaron E. Parsonnet, Arthur C. DeGraff, Clarence E. de la Chapelle, George H. Lathrope

Joseph Skwirsky, Newark

Aaron E. Parsonnet, W. C. Spain, George H. Lathrope

Jesse McCall, Newton

George John Young, Harold S. Hatch, George H. Lathrope

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J. Hamilton Crawford, Tasker Howard, C. F. Tenney

Louis Friedfeld, Brooklyn

William Goldring, Irving J. Sands, C. F. Tenney

Arthur Gerson Hollander, Brooklyn

J. Hamilton Crawford, William H. Lohman, C. F. Tenney

Samuel Millman, Brooklyn

Simon R. Blatteis, Irving J. Sands, C. F. Tenney

Abraham Max Rabiner, Brooklyn

Orman C. Perkins, Harold R. Merwarth, C. F. Tenney

Bernard Seligman, Brooklyn

Henry M. Feinblatt, Tasker Howard, C. F. Tenney

Charles Ford Warren, Brooklyn

Tasker Howard, Carl H. Greene, C. F. Tenney

John James Weber, Brooklyn

Alexis T. Mays, Frank Bethel Cross, C. F. Tenney

Jason Engels Farber, Buffalo

Abel Levitt, J. Frederick Painton, Nelson G. Russell

Harold Theodore Schweitzer, Buffalo

Abel Levitt, Herbert J. Ulrich, Nelson G. Russell

Walter David Westinghouse, Buffalo

Clayton W. Greene, Roy L. Scott, Nelson G. Russell

Michael Bevilacqua, Glendale

Frank R. Mazzola, E. B. Erskine, C. F. Tenney

Ruel Lawrence Alden, Hempstead

Roy D. Grimmer, Louis H. Bauer, C. F. Tenney

Bernard M. Scholder, Mount Vernon

Alvan L. Barach, Norman Strauss, C. F. Tenney

Theophilus Powell Allen, New York

F. Warner Bishop, Lewis F. Frissell, C. F. Tenney

George Jarvis Coffin, New York

J. R. Scott, Oswald R. Jones, C. F. Tenney

Robert Henry Fales Dinegar, New York

Leonard G. Weber, Leander H. Shearer, C. F. Tenney

Herman Louis Frosch, New York

Nathan B. Van Etten, A. S. Blumgarten, C. F. Tenney

Albert Crawford Herring, New York

Walter A. Bastedo, Waldo B. Farnum, C. F. Tenney

Jerome Alexander Marks, New York

John L. Kantor, A. F. R. Andresen, C. F. Tenney

Henry Easton McMahon, New York

J. Hamilton Crawford, Harry E. Ungerleider, C. F. Tenney

Carl Muschenheim, New York

Claude E. Forkner, Henry B. Richardson, C. F. Tenney

Eli Hyman Rubin, New York

Max Pinner, J. Burns Amberson, Jr., David Marine, C. F. Tenney

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 Arthur Robert Sohval, New York  
 Jefferson Jonas Vorzimer, New York  
 James Ivan Mooney, Rochester  
 James William Quinlan, Rochester  
 Charles LeRoy Steinberg, Rochester  
 Katharine Stewart Cook, Troy  
 Hermon Camp Gordinier, Troy  
 Ranaid Edwards Mussey, Troy  
 Harold Jerome Harris, Westport

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 A. Allen Goldbloom, Isidore W. Held, C. F. Tenney  
 David B. Jewett, John J. Finigan, Nelson G. Russell  
 David B. Jewett, John J. Finigan, Nelson G. Russell  
 John J. Finigan, Charles B. F. Gibbs, Nelson G. Russell  
 Crawford R. Green, Stephen H. Curtis, C. F. Tenney  
 Crawford R. Green, Stephen H. Curtis, C. F. Tenney  
 Stephen H. Curtis, Crawford R. Green, C. F. Tenney  
 Lewis A. Conner, Peter Irving, Walter W. Palmer, C. F. Tenney

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 Joseph John Combs, Raleigh  
 Thomas Leonard Umphlet, Raleigh  
 John Sinclair Denholm, Sanatorium  
 T. Preston White, Edward J. Wannamaker, Charles H. Cocke  
 C. C. Carpenter, Hubert B. Haywood, Charles H. Cocke  
 Verne S. Caviness, W. B. Dewar, Charles H. Cocke  
 P. P. McCain, W. T. Rainey, Charles H. Cocke

## NORTH DAKOTA

William Ewart Gladstone Lancaster, William C. Nichols, Harry A. Brandes, Julius Fargo O. Arnson

## OHIO

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 Robert Forgy Hiestand, Cincinnati  
 Harry Edward Landt, Cincinnati  
 Richard Smith Tyler, Cincinnati  
 Raymond John Borer, Toledo  
 H. B. Weiss, Julien E. Benjamin, A. B. Brower  
 Johnson McGuire, John H. Skavlem, A. B. Brower  
 Julien E. Benjamin, H. B. Weiss, A. B. Brower  
 Mark A. Brown, William L. Freyhof, A. B. Brower  
 Frank C. Clifford, John T. Murphy, A. B. Brower

## OKLAHOMA

William Turner Bynum, Chickasha  
 Louis Harry Charney, Oklahoma City  
 James Floyd Moorman, Oklahoma City  
 Philip M. McNeill, Wann Langston, Lea A. Riely  
 Wann Langston, Philip M. McNeill, Lea A. Riely  
 Hugh Jeter, Tom Lowry, Lea A. Riely

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 Donald Edgar Forster, Portland  
 Roger Hunter Keane, Portland  
 G. W. Millett, Frank R. Mount, T. Homer Coffen  
 Homer P. Rush, Laurence Selling, T. Homer Coffen  
 John H. Fitzgibbon, Homer P. Rush, T. Homer Coffen

## PENNSYLVANIA

Hugh Montgomery, Ardmore  
 Allen Wilson Cowley, Harrisburg  
 T. Grier Miller, Charles C. Wolferth, Edward L. Bortz  
 C. E. Ervin, Charles C. Wolferth, Edward L. Bortz

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 Henry Walter, Jr., Lancaster  
 Andrew Wirt Goodwin, Oil City  
 Samuel Bellet, Philadelphia  
 Jack Edward Berk, Philadelphia  
 Julius Hiram Comroe, Jr., Philadelphia  
 Daniel Brown Pierson, Jr., Philadelphia  
 Louis Alexander Soloff, Philadelphia  
 Joseph Bedford Vander Veer, Philadelphia  
 John Day Garvin, Pittsburgh  
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 Harvey M. Watkins, C. Howard Marcy, R. R. Snowden  
 Thomas M. McMillan, Louis B. Laplace, Edward L. Bortz  
 Joseph C. Doane, H. L. Bockus, Edward L. Bortz  
 Simon S. Leopold, T. Grier Miller, Edward L. Bortz  
 John Eiman, George C. Griffith, Edward L. Bortz  
 Charles L. Brown, Edward Weiss, Edward L. Bortz  
 Thomas M. McMillan, Louis B. Laplace, Edward L. Bortz  
 George J. Wright, H. G. Schleiter, R. R. Snowden  
 Augustus S. Kech, W. G. Falconer, R. R. Snowden

## RHODE ISLAND

Raymond Luft, Norwood

Herman A. Lawson, Louis I. Kramer, Alex. M. Burgess

## SOUTH CAROLINA

Thomas Wade Bennett, Columbia  
 Albert M. Eaddy, Columbia

Charles M. Griffith, James S. McLester, Fred Wilkerson  
 J. Heyward Gibbes, Hugh Smith, Kenneth M. Lynch

## TENNESSEE

Bruce Rankins Powers, Knoxville  
 Phillip Thurman Crawford, Memphis  
 James Gilliam Hughes, Memphis

Daniel R. Thomas, R. B. Wood, J. O. Manier  
 Conley H. Sanford, Hugh F. Crawford, J. O. Manier  
 Conley H. Sanford, Hugh F. Crawford, J. O. Manier

## TEXAS

Edwin G. Faber, Tyler

H. Frank Carman, Henry M. Winans, M. D. Levy

## VIRGINIA

Thomas Nathaniel Hunnicutt, Jr., Newport News  
 Thomas Nathaniel Spessard, Norfolk  
 James Porter Baker, Jr., Richmond  
 Nathan Bloom, Richmond

William B. Porter, Edward Lee Alexander, Walter B. Martin  
 Frank H. Redwood, C. L. Harrell, Walter B. Martin  
 Douglas G. Chapman, William B. Porter, J. Morrison Hutcheson, Walter B. Martin  
 Harry Walker, William B. Porter, Walter B. Martin

## WASHINGTON

Frederick Lemere, Seattle

Edwin G. Bannick, George H. Anderson, C. E. Watts

## WEST VIRGINIA

George Russell Crisler, Charleston

Martin Loxley Bonar, G. H. Barksdale, A. H. Hoge

*Fellowship Candidates**Sponsors*

## WISCONSIN

M. Meredith Baumgartner, Janesville  
 Joseph George Bohorfoush, Madison  
 Charles Francis Burke, Madison  
 Ruth Caldwell Foster, Madison  
 Herman Alfred Heise, Milwaukee  
 Kenneth Paul Hoel, Pewaukee  
 Kenneth Charles Kehl, Racine

Vincent W. Koch, William S. Middleton, Rock  
 Sleyster  
 William S. Middleton, Elmer L. Sevringhaus,  
 Karver L. Puestow, Rock Sleyster  
 Chester M. Kurtz, A. R. Barnes, Rock Sleyster  
 Chester M. Kurtz, J. S. Evans, William S.  
 Middleton, Rock Sleyster  
 Arthur J. Patek, C. H. Stoddard, Rock Sleyster  
 H. M. Coon, Oscar Lotz, Rock Sleyster  
 T. J. Pfeffer, William S. McCann, Rock  
 Sleyster

## TERRITORY OF HAWAII

Henry Costill Gotshalk, Honolulu  
 Arthur Van Horn Molyneux, Honolulu

Nils P. Larsen, A. G. Schnack, Harry L.  
 Arnold  
 Nils P. Larsen, William S. Middleton, Harry  
 L. Arnold

## DOMINION OF CANADA

*Manitoba*

Francis Alexander Lavens Mathewson,  
 Winnipeg  
 Charles Hutchinson A'Court Walton,  
 Winnipeg

John M. McEachern, J. Currie McMillan, Fred  
 T. Cadham  
 John M. McEachern, J. Currie McMillan, Fred  
 T. Cadham

*New Brunswick*

Norman Stewart Skinner, St. John

Arthur B. Walter, R. J. Collins, H. A. Farris

## OBITUARIES

### DR. WILLARD C. STONER

Dr. Willard C. Stoner of Cleveland, Ohio, died November 15, 1939 at 62 years of age. Dr. Stoner was educated at Ohio Northern University, Defiance College and Ohio Wesleyan University. He pursued graduate study at the University of Michigan, University of Chicago, Johns Hopkins Hospital, Harvard University, University of Berlin, University of Munich and University College Hospital, London.

In the World War, Dr. Stoner organized a medical unit and served as the medical chief of Base Hospital No. 52. He was staff consultant as well as receiving and evacuating officer at Rimacourt, France. Later he was commanding officer and chief of medical service at Evacuation Hospital No. 3, Army of Occupation, Treves, Germany. At the end of the war he held the rank of Colonel in the Medical Reserve Corps and Commanding Officer of General Hospital 246.

In the death of Dr. Stoner the medical profession of Cleveland lost one of its foremost leaders. In 1918 he was appointed Medical Director of St. Luke's Hospital and played a major rôle in developing the present institution. He visualized the modern hospital as a dominant progressive factor in educating the community in health matters as well as for actual professional training and care of the sick. He was a firm believer in the dictum of providing hospital care for the greatest number of individuals at the lowest possible cost.

Dr. Stoner lived for medicine and from it he derived his greatest joy in life. Early in his medical career, Dr. Stoner realized the importance of scientific research in connection with the practice of medicine. This was evidenced by the fact that he was the first to introduce the Wassermann test to Cleveland. He was the author of numerous publications and addresses before various medical societies. In 1937 an anonymous donor gave St. Luke's Hospital \$10,000.00 to be known as the Willard C. Stoner Fund, to be used in support of medical research and graduate medical education.

Dr. Stoner became a Fellow of the American College of Physicians in 1920 and was certified by the American Board of Internal Medicine in 1937.

In his private practice Dr. Stoner well understood the value to the patient of a serene attitude and he helped many to achieve it. His fine achievements and the blessings that his practice conferred on countless individuals in all walks of life, will remain as a consolation to his many friends and an enduring source of pride to his family.

ROBERT A. READING, M.D. (Associate)

## DR. ALLAN JOSEPH HRUBY

Allan Joseph Hruby died on November 18, 1939, of lobar pneumonia. Dr. Hruby was born in Chicago the 27th of April, 1890. He took his degree in medicine at the University of Illinois College of Medicine in 1913 and subsequently served an internship at the Cook County Hospital from 1913 to 1915. This was followed by a research fellowship at the Wesley Memorial Hospital from 1915 to 1916. He was Instructor in Didactic Medicine at the University of Illinois from 1913-1915; Health Officer, City of Chicago Health Department, 1916-1917; Head Clinic Physician, Municipal Tuberculosis Sanitarium, 1917-1918; Medical Superintendent, Municipal Tuberculosis Sanitarium, 1918-1922; Instructor in Public Health Nursing, School for Home and Public Health Nursing, 1918-1922; Secretary and Member of the Board of Directors, City of Chicago Municipal Tuberculosis Sanitarium; Member of the staff at Cook County, St. Anthony's and Washington Boulevard Hospitals; Consulting Physician, Chicago, Milwaukee, St. Paul and Pacific Railroad Co.; Member, Chicago Medical Society, Illinois Medical Society (Fellow), American Medical Association, Bohemian Medical Society, Chicago Tuberculosis Society, National Tuberculosis Association (Fellow), American Public Health Association, Diplomate of the American Board of Internal Medicine, and has been a Fellow of the American College of Physicians since December 20, 1931.

Dr. Hruby left a host of friends both among his patients and his fellow practitioners. All those who knew him regretted very much his untimely death. He was still in the prime of life and giving excellent service to his patients by whom he will be greatly missed. Dr. Hruby was a man of pleasing manner and approach, well-trained and a hard worker who had established an excellent reputation for himself not only in Chicago but throughout the country, especially among the men who were interested in tuberculosis. The profession and the community have lost a fine physician and a worthy citizen.

JAMES G. CARR, M.D., F.A.C.P.,  
Governor for Michigan

## DR. JOHN WILSON TAPPAN

John Wilson Tappan, M.D., F.A.C.P., El Paso, Texas, died September 2, 1939, at an El Paso Hospital.

Dr. Tappan was born September 12, 1867, at Ogden, Kansas. His academic education was received at the St. Mary's College, Kansas, and at the Massachusetts Institute of Technology. His medical education was begun in 1894 under a preceptor at Roan Mountain, Tenn., and later completed at the Medical Department of the University of Virginia, where he served as demonstrator in Anatomy. He was appointed Interne in the Marine Hospital Service for duty in the immigrant wards of the Long Island

College Hospital, Brooklyn; appointed Acting Assistant Surgeon in 1899, he continued on duty in the Hospital for four years, when he was detailed to Ellis Island for duty in connection with medical inspection of immigrants, until 1906, when he accepted a position as Chief Surgeon with the LaFollette Coal, Iron and Railway Co., LaFollette, Tenn. When this company was about to suspend operations, he again entered the United States Public Health Service, and was reassigned to duty at El Paso, Texas, in 1907.

In addition to this service, Dr. Tappan became quarantine officer in 1910, and during the years 1915 to 1917 he was permitted by the Public Health Service to accept the position of City Health Officer of El Paso, at the request of the mayor and city council, during a typhus epidemic. During the World War, he organized and had charge of the Venereal Clinic established by the United States Public Health Service and the American Red Cross. This clinic, afterwards known as United States Government Clinic No. 5, was established January 26, 1918, and was transferred to the city and county of El Paso, July 18, 1919.

In 1924, Dr. Tappan was made supervisor of the border between the United States and Mexico, and in 1925 had charge of the anti-yellow fever work on the Texas-Mexico border. In 1926 he was assigned to duty at the United States Marine Hospital, Fort Stanton, New Mexico, and in 1929 was assigned the position of Officer in Charge of the San Diego Quarantine Station, Port Loma, Calif. Retiring from the Public Health Service in 1933, Dr. Tappan returned to El Paso, where he became director of the City-County Health Department, resigning in 1938 because of his health. In 1939 the Texas State Medical Association conferred upon him the distinction of Honorary Member.

Dr. Tappan contributed a number of articles to medical literature on subjects in his chosen field of public health. He was a member and ex-President of the El Paso County Medical Society, member of the State Medical Association, and the American Medical Association; the Southern Medical Association, the Medical and Surgical Associations of the Southwest, the Association of Military Surgeons, and the Retired Officers Association, and had been a Fellow of the American College of Physicians since April 7, 1929. His death closed the career of a successful physician and public health executive, who was esteemed by all who knew him.

M. D. LEVY, M.D., F.A.C.P.

Governor for Texas

#### DR. CHARLES CLIFTON BROWNING

Dr. Charles Clifton Browning, F.A.C.P., San Marino, Calif., died September 28, 1939, of lobar pneumonia. He had not been in good health since a cerebral attack during October, 1932.

Dr. Browning was born at Denver, Illinois, in 1861. His family removed to Shelbyville, Mo., where young Browning attended the local high

school and later entered the Christian University at Canton, Mo. He graduated from the University of Missouri School of Medicine in 1883. Following this he returned to Denver, Ill., where he practiced for five years and then took a position as Assistant Physician at the New York City Asylum for the Insane. In 1891 he removed to California, seeking better health, and located first in San Jacinto and later in Highland.

While at the latter location he became interested in the black widow spider and made extensive studies of its habits. He supplied the Smithsonian Institution with its first specimens and his first researches on this subject were published in the *Southern California Practitioner*, August, 1901.

Dr. Browning became Medical Director of the Pottenger Sanatorium, Monrovia, in 1905, remaining five years, when he entered private practice in Los Angeles, his work being limited to tuberculosis. During the following twenty-two years he was an acknowledged leader, not only in his special field of medicine, but in all medical activities. He was one of the group responsible for the adoption and development of the California County Tuberculosis Sanatoria, under supervision of the California State Board of Health, which is said to be accountable for the high standard of care given patients in California public institutions. Dr. Browning, in addition to serving several terms as President of the California Tuberculosis Association, was a Director of the National Tuberculosis Association, a member of the Los Angeles County Medical Association, California State Medical Association, American Climatological and Clinical Association, the Association for the study of Internal Secretions, and many other local and State societies. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1920. He was the author of many articles appearing in leading medical journals.

During the World War he was one of the few men beyond the age limit who were admitted to the service, being assigned as Chief of the Medical Service at Fort MacArthur in 1918-19. From 1918, until his retirement, he was Professor of Tuberculosis in the College of Medical Evangelists and he had been, since 1910, Chief of the Attending Staff of the Tuberculosis Service at the County Hospital.

Dr. Browning took an active part in community matters. His influence as a teacher was far reaching and his students and fellow members in the profession, as well as his patients, felt the imprint of his kindly spirit and sympathetic understanding. He was esteemed by all who knew him.

Courtesy of Edward W. Hayes, M.D., F.A.C.P., and "California and Western Medicine."

#### DR. HERMAN TROSSBACH

Dr. Herman Trossbach died of chronic nephritis with hypertension at the age of fifty-eight at the Hackensack Hospital, on October 1, 1939. Dr.

Trossbach was born in Carlsbadt, N. J., where he lived until he went to Jersey City where he went to High School and then did his college work at night at Cooper Union. He was graduated from the Long Island College of Medicine in 1907 and interned at the Englewood Hospital, Englewood, N. J., 1907-1908. Following this he went with his family to Colorado Springs, Colorado, where he began the practice of medicine. About 1918 he returned to New Jersey and took up practice in Hasbrouck Heights, moving to Bogota about 1923, where he practiced until his death.

He was a quiet scholarly gentleman, not much inclined to social life, and spent most of his spare time with his family and working in his garden. He was well known for his work with dahlias and spoke over the radio on this subject. He was respected by his fellow towns-people, but took no active part in community affairs, though giving considerable time to leadership in his profession.

He was Attending Internist at the Hackensack Hospital, at one time president of its Medical Board, and at the time of his death Director of Medical Service in that institution. He was Attending Physician at the Holy Name Hospital, Teaneck, N. J.

He was a member of the Bergen County Medical Society of which he was president in 1926, the New Jersey State Medical Society, the Association for the Study of Internal Secretions, the American Medical Association, and had been a Fellow of the American College of Physicians since 1928.

In 1913 he married Miss Mine Augustin. His wife and two children survive him.

GEORGE M. KNOWLES, M.D., F.A.C.P., and  
GEORGE H. LATHROPE, M.D., F.A.C.P.,  
Governor for New Jersey

#### DR. CHARLES FALKOWSKY, JR.

It is with sincere regret that The American College of Physicians notes the passing of Dr. Charles Falkowsky, Jr., of Scranton, Pennsylvania, who had been elected to Fellowship in 1928.

Dr. Falkowsky was born in Scranton in 1880. He graduated from the Scranton Business College in 1897, and received his degree of Doctor of Medicine from the University of Pennsylvania School of Medicine in 1901. Dr. Falkowsky's internship was taken at the Kings County Hospital in Brooklyn from 1901 to 1903.

From 1906 to 1912 Dr. Falkowsky was Assistant Physician at the Scranton State Hospital. In 1912 he became Chief Physician, which position he held until the time of his death. He was also Consulting Physician at the Nanticoke State Hospital from 1926 to date. He was Physician at the Mercy Hospital from 1930 to date of death.

During the World War, Dr. Falkowsky was Captain of the Medical Corps, United States Army, and Chairman of the Medical Advisory Board.

Society affiliations include membership in the Lackawanna County Medical Society in which society he was also a former President, Member and ex-Chairman of the Medical Section of the Pennsylvania State Medical Society, Fellow, American Medical Association, Member, American Therapeutic Society, Fellow, The American College of Physicians since 1928.

EDWARD L. BORTZ, M.D., F.A.C.P.,  
Governor for Eastern Pennsylvania

### DOCTOR JOSEPH EDMOND DUBÉ

Dr. Joseph Edmond Dubé, of Montreal, Professor of Clinical Medicine in the University of Montreal for the past nineteen years, died at the Hotel Dieu hospital in Montreal on November 25, 1939.

Doctor Dubé was born in Montreal on March 10, 1868.

He took his primary education at Joliette and then studied medicine at Laval University, Montreal, where he graduated in 1894. He then went to Paris for postgraduate study, receiving the State diploma in 1896.

On his return to Montreal he was appointed to the staff of the Hotel Dieu in 1897.

Very shortly after his return he took an active leading part in the medico-social activities of the Province of Quebec.

His success along these lines was due largely to his winning personality and the esteem in which he was held in this community. In 1903 Dr. Dubé took part in the founding of the two institutions for tuberculosis—The Royal Edward and the Bruchesi Institute. From that date onwards, he played a leading part in all educational work on tuberculosis in the Province of Quebec.

In addition to his work on tuberculosis he was one of the founders of the Montreal Medical Society, and the Goutte de Lait.

He was a director of the medical journal—'Union Medicale du Canada'; a member of the Royal College of Physicians and Surgeons of Canada, and a Fellow of the American College of Physicians.

Furnished through the courtesy of Charles F. Moffatt, M.D., F.A.C.P.,  
Governor for Quebec.

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HARRY EDWARD THOMPSON, M.D.  
INTERNAL MEDICINE AND ARTHRITIS

JAMES DONALD FRANCIS, M.D.  
ORTHOPEDIC SURGERY

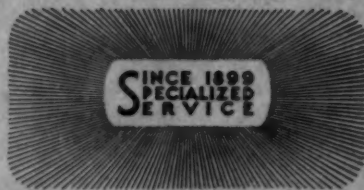
H. F. POTTER  
ROENTGENOLOGY

L. M. STRAND, R.N.  
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CLINICAL LABORATORY

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